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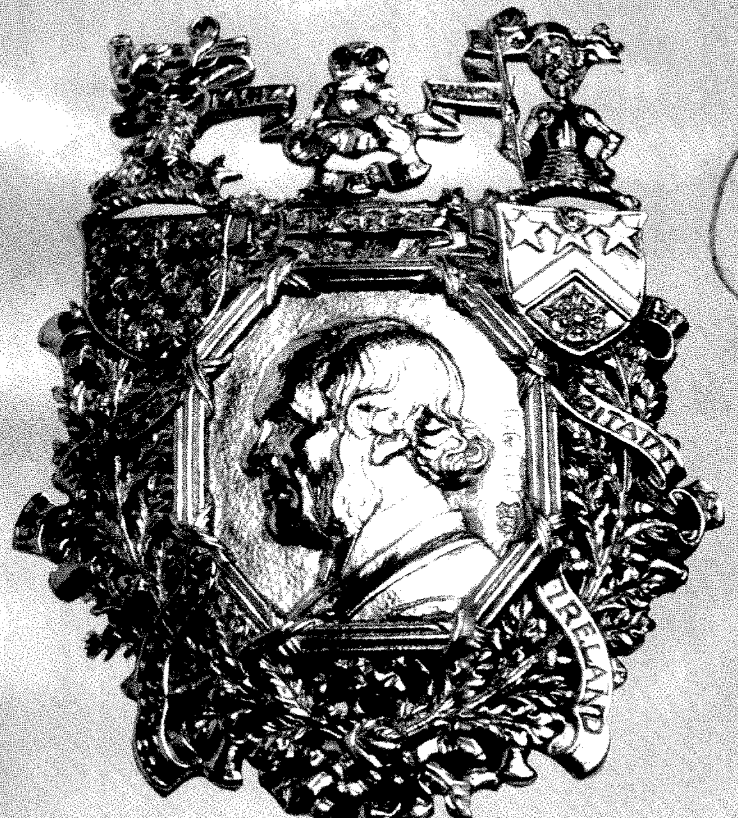

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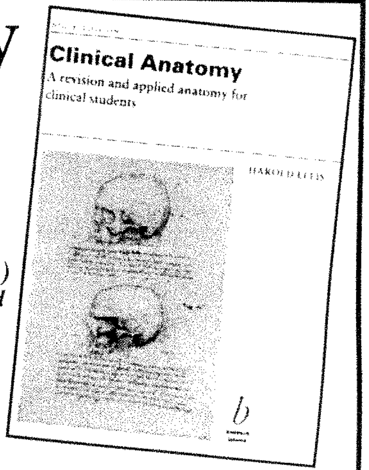

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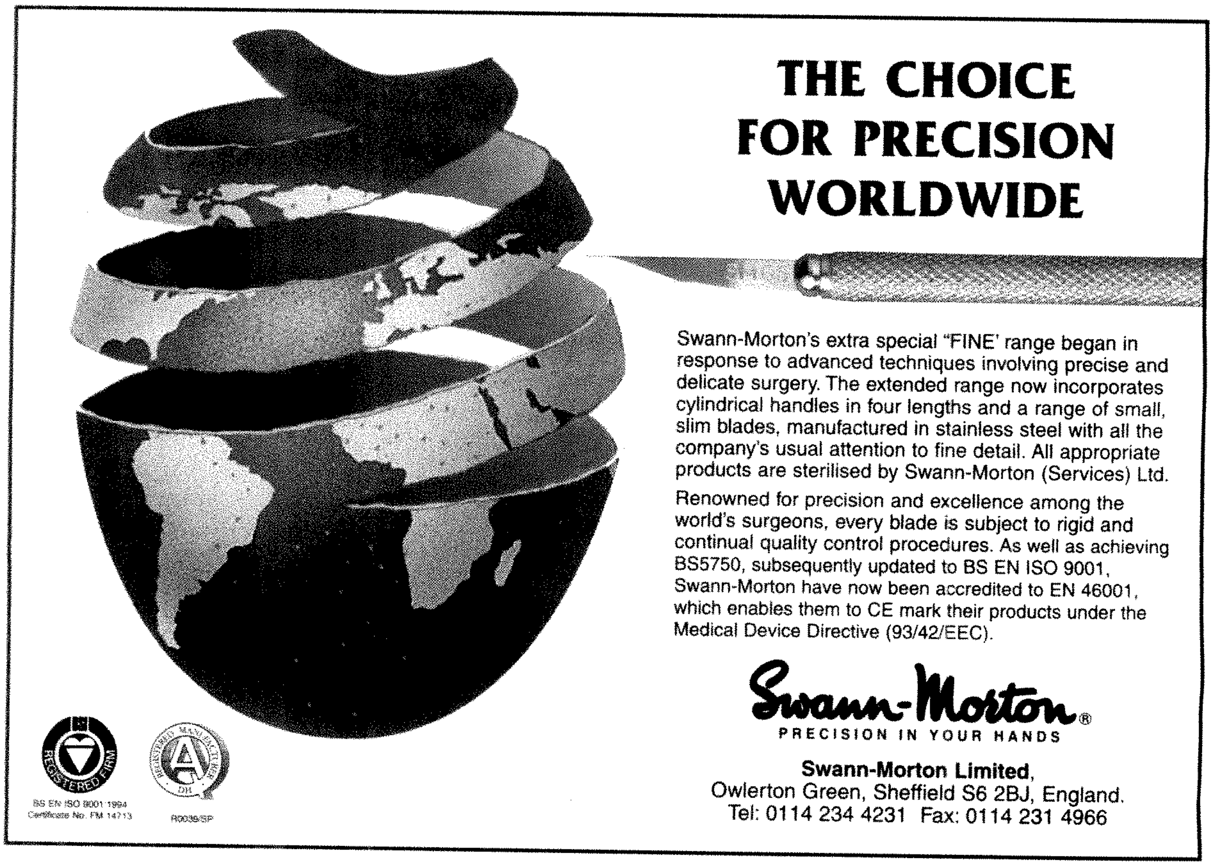

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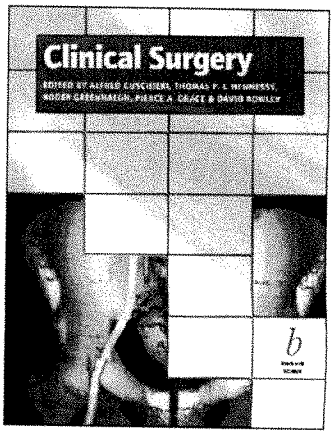

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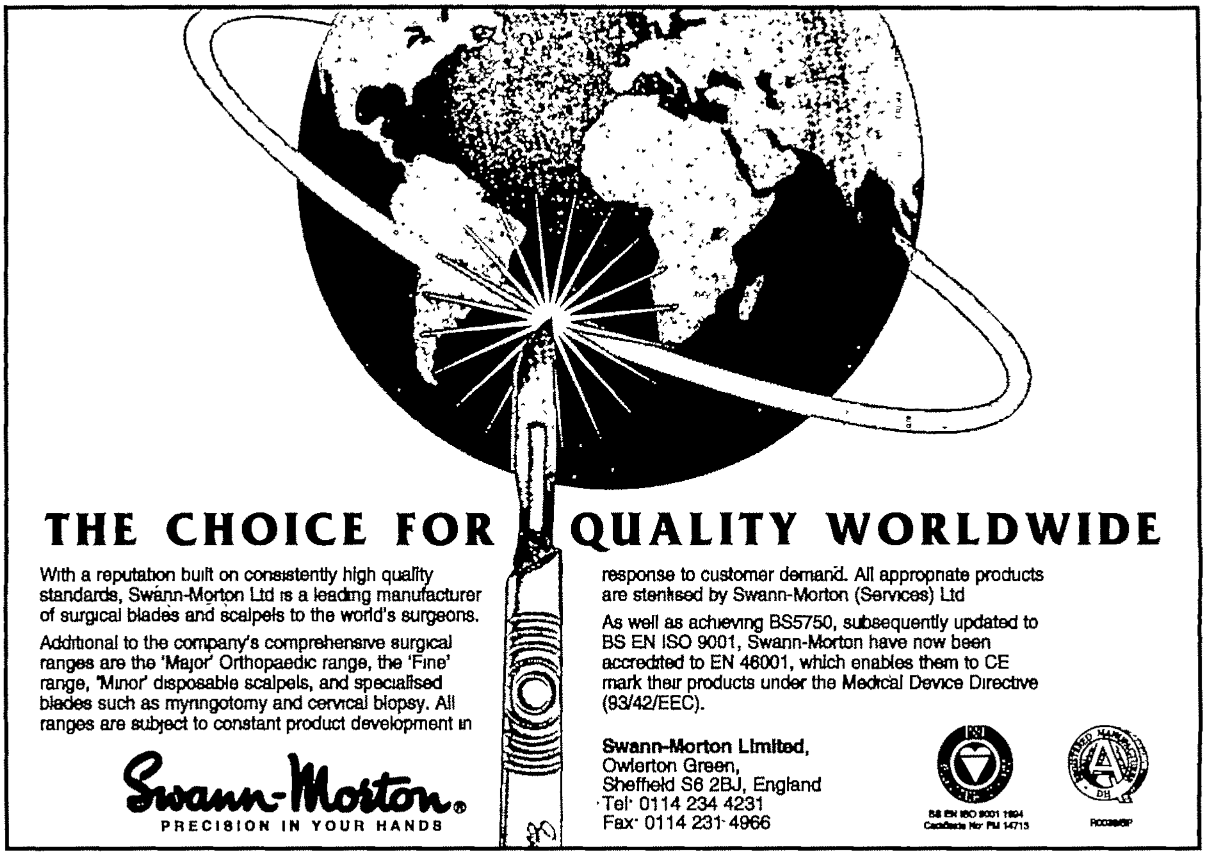

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British Journal of Surgery 1997, 84, 1041–1042

Leading articles

Pain relief in pancreatic disease

The World Health Organization has designated pain relief and palliative care as priorities in its global programme for cancer control. About 80 per cent of all patients with exocrine pancreatic cancer have pain as an initial symptom and practically all will suffer significant pain at some stage before they succumb to the disease[1]. Pain is also the cardinal symptom in chronic pancreatitis and, together with the usual problem of contemporary alcoholism, is the most difficult feature to treat[2]. For some patients with these diseases the pain is so severe that all waking hours are devoted to its control; quality of life is very poor. While these diseases are rarely cured, they can, at best, be rendered symptom free. The management of symptoms should, therefore, be of prime concern in most individuals with these serious pancreatic pathologies.

For both pancreatic cancer and chronic pancreatitis resection of the diseased part of the gland seems to be the most logical treatment and it should always be considered as the first option[3]. Nevertheless, when it is clear that cure is not within reach, pain relief may be provided by simpler procedures directed against the afferent nerves that carry the painful stimuli from the diseased organ to the brain. The sympathetic innervation of the pancreas, including the nerves transmitting pain, depends on cells in the intermediolateral tract of the spinal cord from Th 5 to Th 11. The sympathetic fibres from the cord run to the sympathetic chain and, thereafter, via the major splanchnic nerve (from Th 5 to Th 10) and one or more minor splanchnic nerves (from Th 9 to Th 11) to synapses in prevertebral abdominal plexuses, in the present case specifically to the coeliac ganglion. From a theoretical point of view pancreatic pain might be inhibited by interrupting the nerve fibres anywhere along these paths. In previous years chemical splanchnicectomy was carried out but, although it was not without success, the results were unpredictable[4,5].

As the pain fibres run in the sympathetic chain, pain stimuli can be overcome from within the thoracic cavity where the chain lies immediately subpleurally in a wave-like disposition over the ribs in the posterior mediastinum. These nerves are identified easily at thoracoscopy. Thoracoscopic splanchnicectomy may be performed bilaterally under general anaesthesia using double-lumen endotracheal intubation. In a series of 30 patients treated in Lund, satisfactory stable pain relief was obtained from the first week after surgery to a median follow-up time of 18 months. All but one patient reported clearly reduced pain, but only 17 per cent of individuals reported immediate complete pain relief. One may conclude that thoracoscopic splanchnicectomy appears promising as a relatively simple treatment for severe chronic pancreatic pain[6]. Nevertheless, it must be appreciated that the effect of splanchnicectomy is difficult to assess in such patients because of their preoperative addiction to alcohol and strong analgesics[7]. It seems possible that the results in the prospectively followed group of patients in Lund might have been better if they had not been exposed to strong analgesics for a long time and, indeed, if the duration of the pain had itself been limited.

Those with established chronic pancreatitis or pancreatic cancer do not present with features that are uniformly related to the stage of their disease, or to extrapancreatic secondary symptomatology or to morphological features. This lack of uniformity also influences the pattern of pain and the outcome of attempts at management, not only of symptoms but of the patient as a whole. Initially, the cornerstone of management is a stepwise escalation of analgesics; it is wise to provide patients with full information on their condition and its treatment in order that they themselves may be involved in the management process. At some stage, however, rather than crossing the borderline into narcotic usage or turning to palliative resection, it may be useful to consider other methods of pain control. In the light of what is now known, thoracoscopic splanchnicectomy seems a good option; its precise role will become better defined over the next few years. In those with specific morphological features, such as stricture of the main pancreatic duct near the duodenum, it may be possible to achieve effective treatment by endoscopic stenting of the duct[8,9]. However, the place of this procedure for pain control must be evaluated carefully and compared with other options, preferably in controlled randomized studies. Stenting may also be useful in selected patients with pain due to outflow obstruction in pancreatic cancer.

Today, resectional surgery in those with severe pain due to cancer can be performed with low morbidity and a mortality rate of almost zero[10]. However, the indications for palliative resection as opposed to palliative bypass are still not clear. It is appropriate, therefore, that such operations should, if possible, be performed in centres dedicated to the scientific follow-up of all patients (for at least 5 years)[7]. For the present, the best long-term results of treatment of the pain of chronic pancreatitis and pancreatic cancer are likely to come from a careful appraisal of the patient's situation and a treatment that is tailored to the individual as well as to his or her disease. Prognosis is also related to the attitude of the patient and it may depend as much on awareness of the situation and confidence in the treatment as on specific technical aspects of medical and surgical management.

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Human immunodeficiency virus and lung cancer

Infection with human immunodeficiency virus (HIV) is linked with a variety of neoplastic conditions. The major example is Kaposi's sarcoma which is 2000 times more common in HIV seropositive individuals than in HIV seronegative subjects and is associated with human herpes virus 8 (HHV8)[1,2]. The incidence of non-Hodgkin's lymphoma is increased in those who are HIV seropositive; up to 5 per cent of patients with acquired immunodeficiency syndrome (AIDS) develop this condition[3]. Both the prevalence and severity of intraepithelial, cervical and anal neoplasia is increased in HIV seropositive individuals but the incidence of cervical and anal invasive carcinoma is not, although the risk of anal carcinoma is independently increased in HIV seronegative homosexual men[4]. The human papilloma viruses HPV16 and 18 are more frequently found in HIV seropositive than seronegative homosexual men, presumably accounting for the increased incidence of intraepithelial anal neoplasia, but it is not clear why invasive anal carcinoma is not encountered more frequently[5]. In immunodeficiency states generally, it is only some neoplastic conditions that have an increased incidence. These tend to be conditions associated with oncogenic viruses and this seems to be the case with the immunodeficiency state induced by HIV, in which the profound defect in cell-mediated immunity may result in a breakdown in immune-mediated tumour surveillance. An intact immune system may not only reduce the oncogenic viral load but also recognize and destroy viral antigens on tumour cells. Generally speaking, in immune deficiency states the incidence of carcinoma is not increased and this seems to be the situation with HIV infection.

On page 1068 of this issue of the Journal, Alshafie *et al.* report on a retrospective series of patients with lung cancer, 11 of whom were known to be HIV seropositive and a further 116 of unknown HIV serostatus. The HIV-positive group were younger (mean age 49·7 years) than the HIV-negative group (mean age 62·7 years); adenocarcinoma was commoner in the former group, accounting for 46 per cent of the tumours compared with 35 per cent in the seronegative group; the survival of the HIV-positive group was significantly shorter, suggesting that either lung carcinoma in this group is more aggressive or that the shortened survival was attributable to the HIV disease itself. Of the 11 HIV-positive patients, five of six treated with radiotherapy could not complete the course as they became too ill, a further four patients were too ill for any treatment, and one patient received chemotherapy. Of the 116 patients of undetermined serostatus, 18 underwent surgery, 45 received radiotherapy and 11 received chemotherapy. The HIV seropositive patients were sicker at presentation, most probably because of concomitant AIDS, from which seven of the 11 died.

Despite this report and a number of others, the association between lung cancer and HIV infection remains uncertain. In a study over several years involving 1701 patients with haemophilia, development of lung cancer was no different between HIV seropositive and HIV seronegative patients[6]. Lung cancer developed in 0·09 per cent of the HIV-infected patients and in 0·15 per cent of HIV seronegative individuals. In a smaller study of six HIV seropositive individuals with adenocarcinoma of the lung, it was estimated that HIV infection carried a 14-fold increased risk of lung cancer[7]. However, this study was not controlled for age, sex or smoking habits. A further study containing seven HIV seropositive individuals with adenocarcinoma suggested that they presented with more advanced disease, more extensive chest radiograph abnormalities, and with more physical signs than a control group of HIV seronegative patients[8]. Others have described 21 HIV seropositive patients with lung cancer, half of whom were under 40 years of age and all but one of whom were cigarette smokers: 11 had adenocarcinoma, six had small cell carcinoma, three had squamous cell carcinoma and one had mixed histology with adenosquamous features[9]. In another report of 19 HIV seropositive patients with lung cancer, 16 were smokers and, when compared with HIV seronegative historical control groups, the HIV seropositive patients were younger with a median age of 47 years and had a shorter median survival of only 3 months[10].

On the basis of these small studies, it is not possible to reach a definite conclusion about whether lung cancer is genuinely commoner in persons infected with HIV because of problems of bias and ascertainment. However, on the evidence available, it seems that lung cancer in HIV seropositive individuals tends to present at an earlier age, is likely to be more extensive at presentation and is strongly associated with cigarette smoking. Adenocarcinoma is the commonest histological type and the clinical course tends to be more rapid than in HIV seronegative individuals, probably because of the presence of concomitant AIDS rather than any special behaviour of the tumour itself.

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Review

Systematic review of randomized controlled trials comparing laparoscopic with open appendicectomy

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Background The role of laparoscopic surgery in the management of patients with suspected appendicitis is still debated despite a number of recent randomized controlled trials (RCTs).

Methods A systematic review has been undertaken of all published RCTs comparing laparoscopic appendicectomy with open appendicectomy. Studies were identified through Medline and supplemented with a manual search of relevant journals and meeting abstracts. Data were extracted and analysed according to predefined criteria.

Results Ten studies were identified, seven of which reported results on an intention-to-treat basis. Laparoscopic appendicectomy was associated with a longer operating time (8–29 min), a minimal reduction in hospital stay and, probably, an earlier return to normal activity. It was also associated with a reduced risk of wound infection (odds ratio 2·6) with no increase in other complications. However, bias, particularly resulting from lack of blinding, makes some of these results difficult to interpret.

Conclusion Laparoscopic appendicectomy was associated with some advantages and no obvious disadvantages, apart from prolonged operating time. Future RCTs should be blinded to minimize bias, document adequate follow-up and analyse results on an intention-to-treat basis.

Developments in laparoscopic surgery have generally been greeted enthusiastically by both surgeons and patients. The potential advantages include less postoperative pain, reduced wound size and morbidity, shorter hospital stay and earlier return to normal activity. In many situations there is also the potential for improved diagnostic accuracy. For patients undergoing cholecystectomy, the benefits seemed so convincing that laparoscopic cholecystectomy gained acceptance as the procedure of choice before publication of any randomized controlled trial (RCT). In hindsight, this acceptance may have been premature; recently published RCTs have raised doubts about the benefits[1] and safety[2] of laparoscopic cholecystectomy compared with small-incision techniques, and the incidence of bile duct injury appears to have increased[3,4].

The use of laparoscopy in the management of suspected appendicitis is not new[5]. The accuracy of clinical diagnosis in patients with suspected acute appendicitis is around 70 per cent and is less in women than men[6,7]. Most patients in whom an alternative diagnosis is made at surgery do not require laparotomy[8,9]. Diagnostic laparoscopy allows the correct diagnosis to be reached in patients with suspected appendicitis[10–12], thus reducing the incidence of unnecessary laparotomy and appendicectomy. Laparoscopic appendicectomy may also confer additional advantages over open appendicectomy in terms of postoperative recovery[13–19]. In particular, it has been suggested that wound sepsis may be significantly reduced in patients having laparoscopic appendicectomy[20]. However, many surgeons question whether minimal access techniques significantly alter convalescence from an operation such as open appendicectomy, which is considered relatively minor.

Non-randomized studies have been generally supportive of laparoscopic appendicectomy[13–19] but such comparisons are subject to bias. The RCTs comparing laparoscopic with open appendicectomy have been more conflicting in their conclusions[21–30]. The aim of the present study was to undertake a systematic review of RCTs comparing laparoscopic with open appendicectomy.

Materials and methods

Study identification and selection

A search was made for all studies involving laparoscopic appendicectomy using Medline and *Index Medicus* from January 1989 onwards. References from papers extracted were cross-checked extensively and supplemented by a manual search of major conference proceedings. Papers with a truly randomized study design comparing open with laparoscopic appendicectomy were selected for inclusion. The search identified ten such studies (*Table 1*), nine of which have been published in full[21–29]; one is in abstract form[30]. Eight studies involved both female and male patients and two included male patients only[22,30].

Standard data were extracted from each paper and checked independently by two authors to minimize extraction bias[31]. Additional information was sought from several authors in an attempt to obtain more complete data. Responses to requests for additional information were obtained from two authors. Individual subject data were not sought so the information presented is that obtained from published reports.

Analysis

Disparity between studies, bias and lack of comparable information meant that summary estimates were not

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calculated for most of the outcome measures; however, a descriptive analysis is provided. Wound infection rates were compared using exact methods for stratified tables[32].

Results

The characteristics of the patients enrolled in the ten trials are shown in *Table 1*. The trials ranged in size from 57 to 253 participants. The apparent imbalance in the treatment arms in the study by Ortega *et al.*[28] resulted from a three-way randomization between open appendicectomy and two types of laparoscopic appendicectomy. The two laparoscopic appendicectomy arms have been combined for this review. Two of the trials were in men only[22,30]. The mean or median age ranged from 24 to 32 years.

Three trials excluded patients after randomization. Hansen *et al.*[24] randomized 158 patients, but seven were subsequently excluded as the appendix was not removed in three and conversion to a midline laparotomy occurred in four (two in the open arm and two in the laparoscopic arm). Hebebrand *et al.*[25] excluded nine of the 34 patients randomized to laparoscopic appendicectomy because of conversion to open surgery. Kum *et al.*[26] randomized 72 patients to open appendicectomy and 65 to laparoscopic appendicectomy, but subsequently excluded those in whom the appendix was normal or perforated. Fifteen patients from the open appendicectomy group (11 normal, four perforated) and 13 from the laparoscopic appendicectomy group (ten normal, three perforated) were excluded after randomization. These three trials were excluded from further review on the grounds that an intention-to-treat analysis was not carried out. None of the trials blinded either the patient or the carers to the treatment allocation.

The conversion rate to open surgery among the group randomized to laparoscopic appendicectomy varied from 0 to 20 per cent. The inclusion criteria were similar for six of the seven trials with intention-to-treat analysis; patients had a clinical diagnosis of acute appendicitis and were suitable for either open or laparoscopic appendicectomy. The study by Rohr *et al.*[30] excluded patients with perforated appendicitis and diffuse peritonitis.

Similar outcome measures were used in all seven trials. They included operating time, postoperative hospital stay, postoperative analgesia, complications and wound infections, and the time until return to either work or normal activities.

The difference in mean (or median) operating time ranged from 8·3 to 29 min and was longer for laparoscopic appendicectomy in all studies (*Table 2*). In five of the seven studies, the difference was statistically significant. The definition of operating time and level of experience of the surgeons was not consistently provided. Cox *et al.*[22] and Martin and colleagues[27] defined operating time as the time from incision to wound closure, while the definition used by Tate *et al.*[29] was time from induction of

Table 1 Patient characteristics

Reference	Year	No. of patients		Male (%)		Age (years)		Conversion to open operation§	Positive diagnosis (%)
		LA	OA	LA	OA	LA	OA		
Attwood *et al*[21]	1992	30	32	—	—	20·8 (12–39)*	26·8 (15–67)*	2 (1)	84
Cox *et al.*[22]	1996	33	31	100	100	25 (18–84)*	25 (18–75)*	5 (15)	88
Frazee *et al*[23]	1994	38	37	42	54	30 (10–68)*	28 (10–70)*	2 (5)	84
Hansen *et al.*[24]	1996	85	73	—	—	22 (13–66)†	25 (14–89)†	—	84·8
Hebebrand *et al.*[25]	1994	34	23	—	—	23 (11–84)†	24 (12–67)†	—	—
Kum *et al.*[26]	1993	65	72	33	28	33·1(4·9)‡	30·7(7·3)‡	—	—
Martin *et al.*[27]	1995	81	88	58	58	29*	27*	13 (16)	78·1
Ortega *et al*[28]	1995	167	86	67	78	25*	25*	11 (6·6)	83 0
Tate *et al*[29]	1993	70	70	61	61	31·4*	33·0*	14 (20)	86·4
Rohr *et al.*[30]	1994	30	30	100	100	28 (18–54)*	31 (18–56)*	0 (0)¶	85

Values are *mean or †median (range), or ‡mean(s.d.); §values in parentheses are percentages. ¶Perforated appendix and diffuse peritonitis were excluded before randomization. LA, laparoscopic appendicectomy; OA, open appendicectomy

Table 2 Operating time for trials analysed according to intention to treat

Reference	Year	Laparoscopic appendicectomy		Open appendicectomy		Difference in means	*P*
		n	Operating time (min)*	*n*	Operating time (min)*		
Attwood *et al*[21]	1992	30	61†	32	51†	10	>0·05‡
Cox *et al.*[22]	1996	33	58·9(23·0)	31	50·6(20·6)	8·3	0·13§
Frazee *et al*[23]	1994	38	87	37	65	22	<0·001‡
Martin *et al*[27]	1995	81	102 2	88	81·7	20·5	0·0002§
Ortega *et al.*[28]	1995	167	68(32)	86	58(27)	10	<0·005¶
Tate *et al*[29]	1993	70	70·3(21·9)	70	46·5(4·7)	23·8	<0·001§
Rohr *et al*[30]	1994	30	71(30)	30	42(4)	29	<0·0001¶

*Values are mean(s d.) or †median. ‡Wilcoxon rank sum test; §unpaired *t* test; ¶analysis of variance anaesthesia to the administration of a reversal agent. Standard deviations were not given for two of the six studies which compared means, so a weighted average of the mean operating times could not be calculated. Furthermore, two of the studies used a non-parametric test to compare operating times, suggesting that they were not normally distributed. There is no evidence from any of the studies that different surgeons were used to undertake laparoscopic and open appendicectomy, although it is possible that the level of senior supervision was not always the same for both procedures.

Analgesic requirements and/or postoperative pain were significantly less after laparoscopic appendicectomy in three intention-to-treat studies[21,23,28], whereas the converse was found in none. Postoperative pain and analgesic requirements were assessed in a variety of ways such that pooling of data was not possible. In one study[28], linear analogue pain scores were recorded in a subgroup of 135 patients blinded to the procedure by use of special dressings. In this group pain scores were significantly lower at 24 and 48 h after laparoscopic appendicectomy than at equivalent times after open appendicectomy.

Table 3 compares postoperative hospital stay. This was shorter for the laparoscopic group in five of the six trials that examined this aspect. In four of the trials, the difference was statistically significant. The difference in mean stay ranged from −2·1 to 0·8 days. Ortega *et al.*[28] compared only those patients randomized to laparoscopic surgery with a stapling device with those having open surgery. The other group, in whom endoloops were used, had a mean(s.d.) hospital stay of 3·0(2·7) days, slightly longer than that for the open appendicectomy group. The means for this study were calculated after removal of five patients who stayed longer than 9 days, although the *P* value was calculated with these patients included.

Information on postoperative complications (including wound infections) is provided in *Table 4*. Four of the seven studies with intention-to-treat analysis enumerated particular postoperative complications[21,22,28,29] and all reported wound infections, but definitions of wound infection were not always provided. All the studies, except that of Rohr *et al.*[30], reported a higher number of wound infections after open appendicectomy. The numbers are small but one study found a statistically significant difference in complications[21], and another found a significant difference in wound infections[28], both in favour of laparoscopic appendicectomy. The definitions of wound infection may vary between studies, but it is reasonable to combine information if the definitions and notification procedures were consistent within each study. The pooled odds ratio from all seven studies was 2·6 (95 per cent confidence interval 1·3–5·2), indicating that wound infections are likely to be more common after open than laparoscopic appendicectomy ($P = 0·003$).

In all studies patients were followed up after discharge and information was collected on return to activity (*Table 5*). The definitions of activity varied among the studies and in some several were given. The present authors have used return to normal activity or full fitness where this was given; otherwise return to work was used. Follow-up was complete for two of the studies[23,30]; follow-up rates were not given for two other studies[27,28]. In the report by

Table 3 Postoperative hospital stay for trials analysed according to intention to treat

		Laparoscopic appendicectomy		Open appendicectomy			
Reference	Year	*n*	Postoperative stay (days)*	*n*	Postoperative stay (days)*	Difference in means	*P*
Attwood *et al.*[21]	1992	30	2 (1–7)†	32	3 (1–7)†	−1	<0 01¶
Cox *et al*[22]	1996	33	2·9(0 3)	31	3·9(0·4)	−1·0	0·04**
Frazee *et al*[23]	1994	38	2·8	37	2·0	0·8	>0·05¶
Martin *et al.*[27]	1995	81	2·2	88	4·3	−2·1	0·007**
Ortega *et al.*[28]	1995	78‡	2·2(3·2)§	86	2·8(1·6)§	−0·6	<0 05††
Tate *et al*[29]	1993	70	3·5	70	3·6	−0·1	>0·05‡‡
Rohr *et al.*[30]	1994	30	—	30	—	—	—

*Values are mean(s.d.) or †median (range). ‡Laparoscopy with stapler only; §omitting five patients staying longer than 9 days. ¶Wilcoxon rank sum test; **unpaired *t* test; ††analysis of variance; ‡‡log rank test

Table 4 Wound infections and complications for trials analysed according to intention to treat

		No. of patients		Complications			Wound infections		
Reference	Year	LA	OA	LA	OA	*P*	LA	OA	*P*
Attwood *et al*[21]	1992	30	32	0 (0)	4 (12)	<0·05†	0 (0)	1 (3)	—
Cox *et al.*[22]	1996	33	31	4 (12)	8 (26)	>0 1‡	0 (0)	2 (8)	—
Frazee *et al.*[23]	1994	38	37	3 (8)	2 (5)	—	1 (3)	1 (3)	—
Martin *et al.*[27]	1995	81	88	11 (14)	11 (12)	—	3 (4)	6 (7)	>0 05§
Ortega *et al*[28]	1995	167	86	40 (24)*	18 (21)*	—	4 (2)	11 (13)	<0·05†
Tate *et al.*[29]	1993	70	70	15 (21)	17 (24)	>0·05†	7 (10)	10 (14)	>0·05†
Rohr *et al*[30]	1994	30	30	—	—	—	1 (3)	0 (0)	—

Values in parentheses are percentages *Postoperative complications only. LA, laparoscopic appendicectomy; OA, open appendicectomy Overall, wound infection was more common after open than laparoscopic appendicectomy (odds ratio 2·6 (95 per cent confidence interval 1 3–5·2); $P = 0\ 003$). †Fisher's exact test; ‡χ^2 test; §not specified

Table 5 Return to normal activity for trials analysed according to intention to treat

			Laparoscopic appendicectomy		Open appendicectomy			
Reference	Year	Completion of follow-up (%)	n	Return to activity (days)	n	Return to activity (days)	Difference in means	P
Attwood *et al.*[21]	1992	87	26	21 (5–120)*	28	38 (5–150)*	−17	0·02¶
Cox *et al.*[22]	1996	80	27	10·4(4·7)†	24	19·8(11·8)†	−9·4	0·0005**
Frazee *et al*[23]	1994	100	38	14·0†	37	25·0†	−11·0	<0·001¶
Martin *et al*[27]	1995	—	81	12·2†	88	12·8†	−0·6	0·92**
Ortega *et al.*[28]	1995	—	167	9·0(8·5)†	86	14·0(11)†	−5·0	0·001††
Tate *et al.*[29]	1993	63	46	79§	42	74§	—	—
Rohr *et al*[30]	1994	100	30	18·0(12·0)‡	30	20·0(10)‡	−2·0	0·49††

Values are *median (range) or †mean(s.d.) time to return to normal activity; ‡mean(s.d.) time to return to work; §percentage returned to normal activity at a mean of 3 weeks after operation. ¶Wilcoxon rank sum test; **unpaired t test; ††analysis of variance

Tate *et al.*[29], patients were invited to attend an outpatient clinic 2–3 weeks after operation. Only 63 per cent of patients attended this clinic. Of those who did, similar proportions of patients who had open appendicectomy and laparoscopic appendicectomy had returned to normal activities. The remaining trials all found that patients in the laparoscopic appendicectomy group took less time to return to normal activities on average; the difference was statistically significant in four of the trials[21–23,28]. The mean difference in time to return to activities ranged from 0·6 to 17 days.

Discussion

The relative advantages and disadvantages of laparoscopic and open surgery are measured primarily in terms of quality of life for the patients involved. The studies reviewed here measured this using analgesia requirement, length of stay in hospital, and the time until return to normal activities. Laparoscopy may also provide benefits related to more accurate diagnosis[10–12], so this may be the preferred method even in the absence of differences in quality of life. This applies particularly to females, and males in whom diagnostic uncertainty exists[8,9]. Cost-effectiveness has not been considered in this review, but clearly if there are no important differences in quality of life the cheaper option would be preferable.

The importance of RCTs in comparing the effectiveness of surgical procedures is widely recognized[33]. Adequate control of bias in non-randomized studies is very difficult, and results from non-randomized studies often fail to be reproduced in randomized studies. One group of surgeons has carried out a non-randomized[34] and a randomized study[29] of laparoscopic appendicectomy which reached different conclusions. Because of the likelihood of bias, only RCTs were considered in this review. Several of the randomized trials identified in the literature search did not publish intention-to-treat analyses. While these studies have been listed, they were excluded from the review.

None of the trials was able to blind the patients or any of the health care providers to the type of surgery performed. Blinding is particularly important when the measures of outcome might be affected by the knowledge of treatment allocation. In trials of laparoscopic surgery the potential for bias from lack of blinding is high. Preconceived notions on the part of both the patients and the medical and nursing staff might affect the use of analgesia and the time of discharge from hospital. Discharge may also be affected by hospital policy[35,36]. The speed with which patients return to work and other normal activities may be affected by advice given to the patients after discharge as well as advice given in hospital and their own expectations. Since the general perception is that recovery after laparoscopic surgery is quicker and accompanied by less pain, this tends to bias the results in favour of laparoscopic surgery.

The value of meta-analysis is that it increases the amount of data available for assessment, such that more precise estimates of the measures can be obtained; it cannot reduce biases present in the individual studies. In addition to the bias from lack of blinding, there were other potential biases which could not be evaluated from the information published. These included incomplete follow-up, identification of complications and wound infections, and surgical experience. Bias might arise if the expertise of the surgeons varied between arms of each trial; for example, it may be that laparoscopic appendicectomy was more commonly supervised or performed by experienced surgeons. In addition to the sources of bias, the different ways of reporting outcome (e.g. median (range) *versus* mean(s.d.)) made it impossible to obtain summary estimates and confidence intervals without obtaining further data from the authors of the studies. In the case of wound infections it was possible to calculate a summary P value and, since the amount of data in each study was small, this provided useful additional information. Collection of further information from authors was not pursued vigorously because of the biases that would remain in the other comparisons.

Analgesic requirements were found to be less for laparoscopic appendicectomy in the three intention-to-treat studies which measured this[21,23,28]. Differences in hospital stay reached statistical significance in favour of laparoscopic appendicectomy in four studies, but the magnitude of the difference was small. Indeed, there were greater differences in mean stay between different hospitals than there were between open and laparoscopic appendicectomy in the same hospital. The extent of the underlying pathological process may also have more influence on early convalescence than the type of surgical access. Recent studies have demonstrated the feasibility and safety of early discharge after open appendicectomy[35,36] and applying such a policy may have a greater influence on hospital stay than laparoscopic appendicectomy itself.

Septic complications following appendicectomy are a major cause of morbidity and wound infection is the commonest of these[7]. However, most of the individual RCTs were underpowered to detect a clinically significant difference in wound infection because of their relatively small size. The meta-analysis found that wound infection was significantly more common after open appendicectomy than after laparoscopic appendicectomy, with a pooled odds ratio of 2·6 ($P = 0{\cdot}003$). It is also likely, but not proven, that infection in a smaller wound is less of a problem than infection in a larger wound. The wound infection rate of 8·4 per cent in the open appendicectomy group is in keeping with the published literature, but follow-up procedures were not described for all the studies and so bias due to incomplete information on wound infections cannot be eliminated.

Return to normal activity is an important endpoint but one which is not always easy to measure, nor was it measured in the same way in all of the studies. Assuming internal consistency measures, most studies found in favour of laparoscopic appendicectomy for early return to work or normal activity. However, this comparison may be biased because of the lack of blinding. While at least part of the observed shortened recovery time after laparoscopic appendicectomy may be due to bias, the bias would have to be very marked in order for it to mask a *longer* recovery time after laparoscopic appendicectomy. On the basis of the information contained in these studies, it seems likely that laparoscopic appendicectomy at least does not increase recovery time. Thus, even if there is no difference in recovery time for more people, laparoscopic appendicectomy may be preferable because of the reduced risk of wound infection. Reduction in the incidence or severity of wound infection may be one reason for a faster return to normal activity after laparoscopic appendicectomy.

Operating time was found to be significantly longer for laparoscopic appendicectomy in six of the seven studies, with a range in mean or median differences from 8 to 29 min. The variation may be due to differences in the surgeons' experience, differences in measuring operating time, or differences in technique. However, while there may be cost implications, the current observed differences are not likely to be significant clinically.

In summary, this systematic overview of RCTs of open appendicectomy *versus* laparoscopic appendicectomy has found that the laparoscopic procedure is associated with a longer operating time, minimal reduction in hospital stay, reduced rate of wound infection with no increase in other complications and, probably, an earlier return to normal activity. The published studies were carried out in several different institutions and different countries, so the results should be generalizable to a wide range of settings. However, the results from this review were not as clear as one would wish, mainly because bias, particularly as a result of lack of blinding, makes some of the results difficult to interpret.

The difficulties involved in conducting RCTs of laparoscopic *versus* open surgery are appreciated (indeed one of the others was a co-investigator in a trial included in this review[22]) and the need for blinding creates an additional demand. However, a recent RCT comparing laparoscopic cholecystectomy with a small-incision technique demonstrated that blinding is achievable[1]. This study attempted to blind both carers and patients, and found no significant differences between the groups in hospital stay or return to normal activity. Another trial of laparoscopic *versus* minicholecystectomy, which was not blinded, found differences in hospital stay and return to normal activity[2]. The fact that different conclusions were reached in these two studies demonstrates the need to evaluate the effect of bias on studies of laparoscopic surgery[37]; a lack of scientific precision may lead to the future delivery of suboptimal care. There is still a role for further randomized trials in evaluating the role of laparoscopic appendicectomy. However, future trials must make every possible effort to remove bias by blinding treatment allocation. It has been demonstrated that some degree of blinding is both ethical and feasible in this setting[1].

Addendum

Since preparation of this manuscript, two further randomized trials have been published[38,39]. In a study of 100 men Mutter *et al.*[38] showed no differences in postoperative pain, return of bowel function, time to discharge, or complications between men randomized to open or laparoscopic appendicectomy. Time taken to return to normal activity was not measured. Reiertsen *et al.*[39] randomized 108 patients with suspected appendicitis, but excluded 24 patients who had acute appendicitis from further analysis. For those with appendicitis there was a modest reduction in mean convalescent time in the laparoscopic group of 4·7 days.

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Review

Tumour necrosis factor and inflammatory bowel disease

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Background Tumour necrosis factor (TNF) is a pleiotropic cytokine produced largely by macrophages and T lymphocytes. It has been implicated in the pathogenesis of numerous immunoinflammatory processes. Recently, a number of studies have indicated that anti-TNF antibodies may be of value in the treatment of inflammatory bowel disease.

Method The literature is reviewed regarding the role of TNF in the pathogenesis of inflammatory bowel disease and the results of administering TNF inhibitors.

Results and conclusions TNF may have a role in the pathogenesis of inflammatory bowel disease. The effects of TNF inhibitors are complex and incompletely understood. Anti-TNF antibody strategies may have a role in the treatment of acute exacerbations of the disease but are unlikely to be appropriate therapies for long-term management.

The aetiology and pathogenesis of inflammatory bowel disease (IBD), i.e. both ulcerative colitis and Crohn's disease, remain unknown. The reason why some patients with IBD have frequent relapses or chronic disease remains equally obscure. However, it is clear that the final pathway to disease and tissue damage is mediated via the immune system and T lymphocytes have a pivotal role in the perpetuation of the immunoinflammatory process. In IBD there is evidence of increased activation of both circulating and tissue immune cells (macrophages, neutrophils and lymphocytes), increased synthesis of immunoglobulins and acute-phase proteins, and increased release of inflammatory mediators[1]. This review discusses the role of tumour necrosis factor α (TNF) as an inflammatory mediator in IBD.

Cytokines

Cytokines are immunomodulatory peptides released by numerous cells and have profound effects on immune function. In IBD, most attention has been focused on TNF, interleukin (IL) 1β and IL-6, which are early and proinflammatory mediators in the cytokine cascade. IL-1β is a powerful activator of neutrophil and macrophage function; in IBD the serum concentration is raised and production by immune cells isolated from the colonic wall is increased[2,3]. The concentration of IL-6, a stimulant of the acute-phase response, is raised in serum[4] but not in stool samples[5] from patients with active IBD. The concentration of IL-10, an inhibitory cytokine, is also raised in the plasma in active IBD. It is postulated that increases in IL-10 concentration are reactive to an excessive release of the earlier, proinflammatory, components of the cascade[6]. Of all the cytokines, TNF has received most attention from investigators into IBD. This interest has been heightened recently by the development of TNF inhibitors which may be useful agents in the treatment of IBD.

Synthesis and release of tumour necrosis factor

TNF, a 157-amino-acid protein, is synthesized predominantly by cells of the monocyte line and by T lymphocytes. In health, TNF is not easily detected and, even in disease, it is found only in picogram amounts. TNF is released in response to a variety of exogenous and endogenous (mostly cytokine) stimuli. Components of the Gram-negative bacterial cell wall, particularly endotoxin (lipopolysaccharide (LPS)), lipid A and muramyl dipeptide, are potent stimuli of TNF release. Gram-positive organisms, yeasts and some viruses can also induce TNF release from cells of the macrophage line[7,8]. Control of TNF secretion is also influenced by proinflammatory and anti-inflammatory cytokines; for example, interferon γ is an important synergistic stimulant for TNF production[9], whereas TNF production is suppressed by IL-10.

Mechanism of action of tumour necrosis factor

For TNF to exert any effect on its target cell it must become complexed to the cell membrane at specific receptor sites. Two distinct populations of these have been characterized. They are transmembrane transport proteins with molecular masses of 55 and 75 kDa, and have been named TNF receptors (TNFRs) I and II[10,11]. These proteins may be cleaved at the cell membrane to release their extracellular domains into the bloodstream as soluble TNFRs (sTNFRs). These exist in a 1000-fold molar excess compared with TNF and some uncertainty still exists about their exact biological function[12,13]; sTNFRs may facilitate the presentation of TNF to target cells or they may remove biologically active TNF from the serum and prevent detrimental overstimulation of immune cells. They may, in fact, exert both of these functions with the particular one exerted depending on the TNF concentration. During periods of excessive TNF production, sTNFRs bind TNF protecting the host and then provide a reservoir from which small amounts of TNF may be released[14]. Before the purification of sTNFRs, Foley *et al.*[15] described a factor in the serum and

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urine of patients with active Crohn's disease which inhibited the cytotoxic effect of TNF in a bioassay; it is possible that this is an effect of sTNFRs.

The wide variety of effects that TNF exerts includes activation of lymphocytes, neutrophils, eosinophils, fibroblasts, chondrocytes and endothelial cells[16]. It is cytotoxic to virus-infected and transformed cells, and in a more general way is felt to mediate the hypotensive response to sepsis and the severe cachexia seen in advanced malignancy (reflected in its original alternative name 'cachectin')[17]. In addition to shock, animals given recombinant TNF develop ischaemic necrosis in the small bowel[18]. This may represent a direct toxic effect mediated through the production of platelet activating factor. In IBD it has been postulated that one of the mechanisms through which corticosteroids exert their anti-inflammatory effect is by inhibition of platelet activating factor transcription[19].

Assay of tumour necrosis factor

There are considerable problems in attempting direct comparison between absolute values for TNF concentrations reported in different studies. These problems are highlighted in a review of commercially available cytokine assays sponsored by the World Health Organization[20]. The recovery of TNF from any fluid is dependent on the antibody and assay system used. In general terms, competitive immunoassays will usually recover more TNF from a system than a bioassay, although comparisons between immunoassays produced by different companies are not possible[21]. Bioassays will be affected to a greater extent by the presence of endogenous inhibitors such as acute-phase reactants, autoantibodies to TNF and sTNFRs[22,23]. Immunoassays will, therefore, reflect the total amount of TNF in a system whereas bioassays will give some indication of the *in vivo* effect of TNF. While there are merits to each assay system, it may be useful to obtain results from both methods in a single study.

Does tumour necrosis factor have a pathogenic role in inflammatory bowel disease?

Studies of patients with major trauma, burns and sepsis have revealed that the cytokine cascade modulates many aspects of immune activation. It was therefore logical that the role of these cytokines should be investigated in chronic inflammatory conditions, such as IBD, in which immune dysfunction is implicated in pathogenesis.

Tumour necrosis factor and models of colitis

In a trinitrobenzene-sulphonic acid (TNBS) hapten-induced model of colitis in the rat, faecal TNF concentrations are raised, and these correlate with severity of colonic inflammation and the degree of systemic inflammatory response, as measured by changes in acute-phase reactants and effects on extracolonic viscera[24]. However, no increase in circulating TNF concentration was found in this model[25], nor in another type of hapten-induced colitis effected in rabbits using dinitrochlorobenzene[26]. The cotton top tamarin is a New World primate which may develop colitis when kept in captivity. This disease closely resembles IBD clinically, histologically and in its progression to neoplasia. In animals with active colitis faecal TNF concentrations are raised[27].

Infective enterocolitis

Faecal TNF concentrations measured by enzyme-linked immunosorbent assay (ELISA) are increased in patients with *Shigella* enteritis, but not in patients with *Salmonella* or viral enteritis[28].

Inflammatory bowel disease

In children with IBD, stool concentrations of TNF measured by ELISA are raised and correlate with severity of colitis[29]. The relationship between raised luminal TNF concentration and disease activity was confirmed in a longitudinal study in adults by Casellas *et al.*[30]. In this study of patients with ulcerative colitis, rectal dialysates were taken and TNF concentrations assayed by ELISA in the effluent fluid. TNF was detected during acute disease but fell to undetectable levels following resolution of macroscopic inflammation. It would, therefore, appear that an increase in luminal TNF concentration may act as a marker of ongoing colonic inflammation and damage. Since faecal TNF concentrations are raised in *Shigella* enteritis and experimental colitis, increased faecal TNF concentrations are not pathognomonic of IBD.

In studies of children with IBD, the relationship between serum TNF concentration and disease activity has not been consistent. Murch *et al.*[31] found a strong correlation using an ELISA method between serum TNF and disease activity, degree of growth suppression and weight loss in colonic Crohn's disease and ulcerative colitis. They did not demonstrate raised serum TNF concentrations in patients with isolated small bowel Crohn's disease. These findings led the authors to suggest that TNF suppressed growth hormone synthesis and this, in turn, mediated the growth failure seen in these patients. However, Hyams *et al.*[32] showed no increase in serum TNF concentration, even in severe disease, and no correlation with growth suppression using a radioimmunoassay. The only significant methodological difference in these studies was the method of assay for TNF. In adult studies Nielsen *et al.*[33] demonstrated an increased serum TNF level in Crohn's disease but not in ulcerative colitis using an ELISA technique. Again using an ELISA method, Gardiner *et al.*[34] detected TNF in the serum of 40–45 per cent of patients with active IBD (both types) and showed that the likelihood of detecting TNF in serum was increased with increasing severity of disease. Sategna-Guidetti and colleagues[35] reported a strong correlation between serum TNF concentration and disease severity using a bioassay. In contrast to other studies they also found raised TNF concentrations in 47 per cent of patients in remission.

These apparently conflicting results can be explained in several ways. First, TNF release may be pulsed because of rapid suppression. IL-10 is known to suppress TNF production and its level is raised in IBD[36,37]. Second, TNF may initiate inflammation but play little role in the development of chronic disease. Third, if TNF is rapidly complexed to circulating receptors or other inhibitors after release its detection may be made difficult[38]. Finally, TNF is known to act in a paracrine way and serum concentrations may be a very poor indicator of its biological effect, which is predominantly exerted on cells close to the cell from which it is released. On currently available evidence, it is not possible to say which of these hypotheses is correct.

The implication from the high faecal TNF concentration in IBD is that TNF is released from cells in, or closely associated with, the mucosa. Immunohistochemical methods have been employed to identify the cells synthesizing TNF. Different patterns of staining for TNF have been shown between Crohn's disease and ulcerative colitis. In both diseases there was staining of cells with the morphological appearance of macrophages in the submucosa. In the former a second population of cells, thought to be T lymphocytes, stained positively in the lamina propria[39]. There is no evidence of colonocyte staining for TNF in either disease[40]. In another study, clinically successful treatment with elemental diet, 5-aminosalicylate derivatives or prednisolone did not reduce the number of TNF-positive cells in rectal biopsies. However, a reduction was noted after treatment with cyclosporin A. Thus the absolute number of TNF-positive cells appears to correlate poorly with disease activity[41].

At an ultrastructural level, using immunogold electron microscopy, TNF has been detected in seven separate cell types (fibroblasts, eosinophils, macrophages, mast cells, colonic epithelial cells, neutrophils and Paneth cells) in the colonic mucosa of patients with Crohn's disease[42]. In this study increased staining for TNF was found in the lipid bodies of all cell types. In eosinophils and Paneth cells TNF was present in secretory granules. There was significantly increased staining in the extracellular space around eosinophils, mast cells and macrophages. Only in neutrophils was TNF demonstrated in the Golgi apparatus. During this study all patients had inactive disease. Therefore no conclusions can be reached about changes in TNF in various subcellular sites and their relationship to disease activity.

In functional studies of mononuclear cells derived from the lamina propria of the colon, there was no difference in basal TNF secretion between controls and areas of microscopically and macroscopically normal colon from patients with ulcerative colitis and Crohn's colitis. After stimulation with mitogen, lamina propria mononuclear cells from patients with IBD, irrespective of disease activity, produced more TNF than controls. However, cells from inflamed areas had significantly increased basal TNF production[43].

When peripheral blood monocytes were stimulated with either LPS or T cell activators (anti-CD3 and anti-CD28) there was no difference in TNF production between cells from patients with Crohn's disease and controls[42]. Cells from patients with ulcerative colitis produced less TNF than those from either of the other two groups. This study supports the hypothesis that the major source of TNF is from cells associated with the bowel mucosa rather than circulating immune cells[44,45]. Despite the increase in faecal TNF and increased basal secretion of TNF from lamina propria mononuclear cells there is no evidence of increased TNF messenger RNA from patients with Crohn's disease[46].

Tumour necrosis factor receptors and inhibitors

Attention has also been focused on sTNFRs in patients with IBD. Stronkhorst *et al.*[47] have described an increased level of sTNFRs in the serum of patients with active Crohn's disease. An increase in the ratio of TNF to sTNFRs has been described in patients with such active disease and it is suggested that it is this ratio rather than the absolute level of TNF which determines disease activity[48]. If this is the case then some important factor in the relationship between TNF and its receptors remains undefined, as sTNFRs were always present in 1000-fold molar excess. TNFRs have been shown to be present in remarkably constant concentrations in health, varying only in acute inflammatory episodes[49] when they behave like acute-phase reactants closely following the course of the disease. Being of low molecular mass, sTNFRs are excreted in urine. They have been detected in the urine of patients with IBD and their concentrations correlate with disease activity. It has therefore been suggested that measurement of urinary concentration of sTNFRs should be used as a method of objectively monitoring disease severity in IBD[50] in place of the more usual acute-phase proteins (C-reactive protein and α1-acid-glycoprotein)[51].

In other chronic inflammatory processes, autoantibodies to TNF have been identified, and it has been speculated that they attenuate the proinflammatory effect of TNF in these diseases[52]. To date, no information is available on their impact on the course of IBD.

Therapeutic possibilities for tumour necrosis factor inhibition

A number of agents have an anti-TNF effect and indeed corticosteroids, widely used in the treatment of IBD, have a potent inhibitory effect on TNF production at transcriptional and translational levels[53]; sulphasalazine inhibits TNF binding to its receptor[54]. However, the biological importance of such observations is uncertain as steroids and aminosalicylates have such a wide variety of effects on many cellular functions[55].

Lactulose is a synthetic disaccharide used in the treatment of hepatic encephalopathy and as a laxative. This agent has anti-TNF effects *in vitro*[56] and has been shown to reduce the mortality rate after surgical insult in an animal model of obstructive jaundice[57]. However, it is difficult to determine whether this improved survival was due to an anti-TNF effect, inhibition of endotoxin or to changes in the enteric microflora. In a rat hapten-induced model of colitis, lactulose reduced systemic endotoxaemia without reducing colonic or systemic inflammation[58]. It has been suggested that, because of its effects on endotoxin and enteric bacteria, lactulose is an agent which should be studied in the human setting[59]. However, because of the diarrhoea it causes lactulose is unlikely to be popular with IBD sufferers.

Pentoxifylline is a xanthine derivative which inhibits TNF production by macrophages *in vitro*; it has been shown to reduce the systemic inflammatory response in experimental peritonitis[60]. When pentoxifylline was given to patients with Crohn's disease who were unresponsive to conventional treatment, in doses large enough to inhibit peripheral blood monocyte TNF production, no clinical improvement was noted[61,62].

Recently a number of anti-TNF antibodies have been developed which are suitable for use in humans. In rheumatoid arthritis, in which high concentrations of TNF are present in the inflamed synovium, treatment with anti-TNF antibodies improved clinical and biochemical variables of disease activity[63]. In hapten-induced models of colitis three accounts of treatment with anti-TNF antibodies have been published (*Table 1*[64–66]). The differences

Table 1 Antitumour necrosis factor antibody treatments in experimental colitis

Reference	Year	Model	Timing*	Colon damage	Outcome	Other findings
Neilly *et al*[64]	1995	Rat TNBS	Before	Acute	No improvement	Serum α_2-macroglobulin and IL-6 decreased
Videla *et al.*[65]	1996	Rat TNBS	Before and after	Acute Chronic	No improvement Improved	Unchanged colonic eicosanoid release Reduced colonic eicosanoid release
Neurath *et al*[66]	1996	Mouse TNBS	After	Acute Chronic	Improved Improved	Fewer CD4-positive LPMNCs; LPMNC cytokine production decreased

*Timing of antibody administration with respect to induction of colitis. TNBS, trinitrobenzene–sulphonic acid; IL, interleukin; LPMNC, lamina propria mononuclear cell

Table 2 Results of anti-tumour necrosis factor antibody treatments in ulcerative colitis

			No. of patients		
Reference	Year	Antibody	Treatment group	Placebo group	Outcome
Baert *et al.*[69]	1996	cA2	2	0	No improvement at 4 weeks
Evans *et al*[70]	1996	CDP571	15	0	Clinical and endoscopic improvement at 4 weeks
Sands *et al*[71]	1996	cA2	8	3	TW decreased at 2 weeks in four patients

TW, Truelove and Witts criteria

Table 3 Results of anti-tumour necrosis factor antibody treatments in Crohn's disease

			No. of patients		
Reference	Year	Antibody	Treatment group	Placebo group	Outcome
Van Dullemen *et al.*[72]	1995	cA2	10	0	CDAI and CRP levels lowered; colonoscopic improvement
Baert *et al*[69]	1996	cA2	4	2	Improved histologically
McCabe *et al*[73]	1996	cA2	20	0	Improved endoscopically
Stack *et al.*[74,75]	1996, 1997	CDP571	20	10	HBI and CDAI decreased; CRP and α_2-macroglobulin levels lowered
Baert *et al.*[76]*	1996	cA2			Histological improvement; HLA-DR expression decreased; fewer CD68-positive macrophages

*Thirteen patients were recruited but the numbers of treated and control subjects were not specified. CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein, HBI, Harvey Bradshaw Index; HLA, human leucocyte antigen

between results in acute and chronic models may be explained if the initial chemical injury due to the ethanol is unaffected by anti-TNF antibody, whereas the more chronic immunologically mediated response to TNBS is modulated by anti-TNF treatments. Intramuscular administration of anti-TNF antibody CDP571 to cotton top tamarins with colitis led to significant improvement in their disease, as gauged by direct inspection of the colon at sigmoidoscopy and histological scoring[67]. This may be a more relevant model for IBD as there is no initial chemical injury.

In the human situation Derkx *et al.*[68] were the first to report clinical improvement in Crohn's disease after use of anti-TNF antibodies in a child who was unresponsive to standard therapies. A series of reports has since followed, documenting the use of anti-TNF antibody in IBD; most of these have been uncontrolled studies (*Tables* 2[69–71] and 3[73,74,76]). Two studies have been reported in full. The first[72] was of patients with Crohn's disease who were unresponsive to conventional treatments and who were treated with a single dose of 10 or 20 mg/kg of an anti-TNF human/mouse chimeric monoclonal antibody (cA2) by intravenous infusion. Although this study showed an encouraging improvement in symptoms and colonoscopic appearance, all patients relapsed within a year. As this study involved small numbers, was uncontrolled, and the patients continued conventional treatment throughout the study period, no definite conclusions can be drawn from it. A large controlled multicentre study enrolling more than 100 patients has recently been completed in the USA but to date the results have not been published[77].

The only randomized double-blind study published to date has used the CDP571 antibody in patients with moderately active Crohn's disease[75]; it was shown that a single dose of this agent could reduce activity indices and serum acute-phase reactant concentrations. However, the effect was rather short lived (around 2 weeks) and seemed to depend on the presence of the antibody in the patients' serum. Six of 20 patients achieved remission, defined as a Crohn's disease activity index of less than 150, and three of these remained in remission at 8 weeks. In the control group, three of ten patients had entered remission by the end of the study, underlining the difficulties with any assessment of a novel therapeutic agent in IBD. Again the protocol in this study allowed for the continuing use of 5-aminosalicylates, steroids and azathioprine during the study period.

While these studies (*Table 2* and *3*) show an encouraging initial improvement in disease activity and an absence of severe toxic reactions, they all have short follow-up periods and most document relapse within these periods. Even in the short term, it is difficult to comment on the effectiveness of such treatments; further work is needed to ascertain the usefulness and safety of long-term therapy.

When these results are compared with those of previously described pentoxifylline therapy, it appears that there is more to the antibody treatment than simply neutralization of circulating TNF. It has been assumed that the effect of the anti-TNF antibodies in these studies results from direct antagonism of circulating or cellular TNF. However, pentoxifylline inhibits TNF production without clinical effect in Crohn's disease and, since the half-life of the antibodies is less than a week, it seems unlikely that simple binding of a cytokine for this short period could modulate disease activity for up to 6 months, as has been described with the cA2 antibody. There is evidence that cA2 has a profound effect on T lymphocytes through both an antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism and a complement-dependent cytotoxicity mechanism. Recent work has shown that T helper 1 responses are downregulated in patients with Crohn's disease treated with cA2, supporting the view that factors other than direct antagonism of TNF effects may be important[78].

The two principal antibodies that have been used in clinical trials are derived from different immunoglobulin G subclasses: cA2 is derived from the $\gamma 1$ subclass which fixes complement and mediates ADCC; CDP571 is derived from the $\gamma 4$ subclass which does not fix complement avidly and does not have a role in ADCC. CDP571 is, therefore, likely to act by blocking circulating TNF and binding to membrane-bound TNF modulating cellular responses, whereas cA2 will have the additional effect of mediating complement-dependent lysis of immune cells expressing TNF on their surfaces[79,80]. Other workers have demonstrated that massive infusion of pooled gamma globulin can improve refractory IBD. The reasons for this improvement are not clear but may involve modulation of endogenous antibodies, macrophages and inhibition of inflammatory mediator production. It seems unlikely that anti-TNF antibody therapy acts in such a non-specific way as a clinical effect from pooled antibody infusion was demonstrated only after several grams had been infused[81].

In the treatment of rheumatoid arthritis more work has been done on the practical aspects of anti-TNF antibody treatments. It has been demonstrated that anti-TNF strategies are a very effective therapeutic option in the short term, both in respect of the local response at acutely inflamed joints and as systemically measured by acute-phase responses[82]. There has been little evidence of tachyphylaxis and, when the cA2 antibody was used, immune responses against it were uncommon. However, a number of infective events felt to be related to the treatment occurred and some patients developed antinuclear or anticardiolipin antibodies[83,84]. Although no complications directly attributable to these autoantibodies were described, it will be necessary to follow treated patients closely over a number of years to ensure that autoimmune disease does not occur. In the short term, only 50 per cent of the patients originally enrolled were able to complete four cycles of treatment, the others having been withdrawn because of intolerance, infective complications or the development of autoantibodies.

The most recent development in the field of anti-TNF treatment has come from the characterization of enzymes responsible for cleavage of monomeric TNF (17 kDa) from its larger inactive promolecule (26 kDa). These have been described as metalloproteinases as they depend on the presence of zinc for their activity[85]. Efforts are being made at present to design inhibitors of these enzymes and thus prevent cleavage of TNF and its liberation as an active agent. Already some agents have been identified with potent inhibitory effects *in vitro* which appear to be very specific for TNF production (IL-1 and IL-6 being unaffected)[86]. Such compounds, when administered simultaneously with an LPS challenge, attenuate TNF production and increase survival in a murine model of endotoxaemia[87]; as yet there is no experience with their use in models of IBD.

Conclusions

Cytokines are undoubtedly important mediators in the development of IBD. Despite intensive research, considerable gaps remain in our understanding of the role of TNF in these diseases. It is still not clear which population of cells is the major source of TNF release during active disease. The fact that raised faecal TNF concentrations have been found consistently in patients with IBD but are also raised in *Shigella* infections suggests that the cell of origin is in the colonic wall rather than circulating immune cells. Since levels of TNF are raised in both conditions, its production may well be of pathogenic significance, but it is certainly neither specific for IBD nor the primary event in its development. TNF production is much more likely to be a response to an, as yet, undefined immunological stimulus. The contradictory evidence obtained from assays of TNF in serum may be explained by differences in assay technique, but it may also reflect the problems of viewing only one component of a complex system in isolation, when it is the overall pattern of interactions between stimulants and inhibitors of the response which is important. The precise relationships between the proinflammatory and anti-inflammatory cytokine cascades have not been defined adequately in IBD. It also appears that a therapeutic response can be achieved in IBD without reducing the number of TNF-positive cells in the bowel wall.

Caution must be exercised with regard to therapies which rely on non-specific inhibition of the many effects of TNF. TNF is important in the response against infective agents and cells that have undergone malignant change, and any treatment strategy which relies on long-term blanket inhibition of its effects cannot be free from the worry that these vital defence mechanisms are being undermined. The difficulties in administering monoclonal antibodies in the long term are significant, especially with regard to cost and patient inconvenience resulting from the need for parenteral administration of the antibody. Because of their very short half-life, sTNFRs are not appropriate therapeutic options, although the affinity and half-life of these receptors has been improved significantly by complexing them with polyethyleneglycol or immunoglobulin heavy chains[88,89]. If, however, a significant part of the biological effect of these antibody treatments results from ADCC leading to immune cell destruction and reducing expression of other proinflammatory cytokines, treatments directed solely against circulating TNF are unlikely to be as effective as has been hoped. It is possible that anti-TNF antibody treatments will find their place as short-term emergency measures for the control of fulminant disease and that long-term treatment will be directed towards modifying or removing the immunological stimulus which results in TNF overproduction in the first place.

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Review

Fibrinogen, fibrin turnover, endothelial products and vascular surgery

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Background Raised plasma fibrinogen levels and markers of fibrin turnover or endothelial disturbance are associated with cardiovascular disease.

Methods This is a critical review of the English language literature relating to fibrinogen, fibrin degradation products and endothelial products in peripheral arterial disease and revascularization surgery.

Results and conclusion Altered levels of plasma fibrinogen and endothelial products are associated with atherosclerosis and some studies have shown an association with poor outcome following revascularization surgery. Randomized clinical trials of therapies that modify thrombotic pathways in patients undergoing surgery for peripheral arterial occlusive disease are therefore required.

Thrombosis is a major feature of atherosclerotic arterial disease[1,2]. The formation of thrombus is dependent on the interaction of many factors (*Fig. 1*), including those of the clotting cascade, activation of which results in formation of insoluble cross-linked fibrin from its plasma precursor, fibrinogen. Cross-linked fibrin and platelets are the major constituents of thrombus. Lysis of this fibrin generates cross-linked fibrin degradation products (FDPs) which include the D-dimer FDP (a specific product of the lysis of cross-linked fibrin). Fibrinolysis is one means by which excessive thrombus production is prevented in normal circumstances. In addition, the endothelial products tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI) have a central role in thrombosis and fibrinolysis; tPA promotes the formation of the fibrinolytic agent plasmin from its inactive precursor, plasminogen, while PAI inhibits this process (*Fig. 1*). von Willebrand factor (vWF), produced by vascular endothelium, has a crucial role in platelet–vessel wall interactions, being an absolute requirement for the formation of occlusive arterial thrombi at sites of endothelial injury[3].

Fibrinogen has been identified as a major risk factor for the development of ischaemic heart disease in a number of prospective population studies[4–6]. There have also been

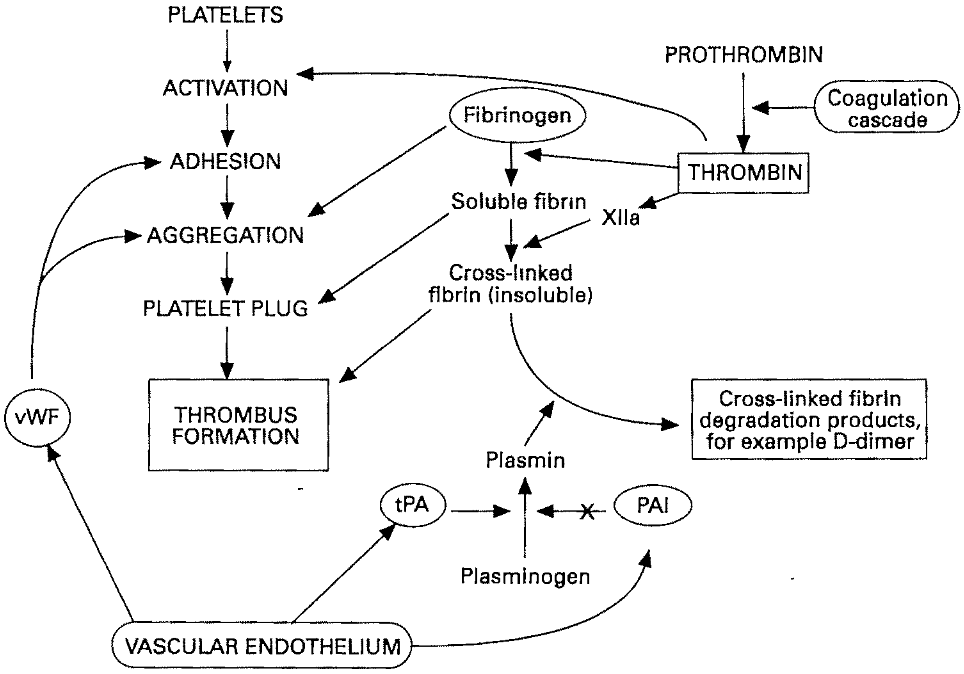

Fig. 1 Summary of the role of fibrinogen and endothelial products in thrombus formation and lysis. Endothelial products and fibrinogen are encircled. PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; vWF, von Willebrand factor

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studies linking fibrinogen levels to peripheral vascular disease. Dormandy and colleagues[7] demonstrated that blood viscosity and fibrinogen levels were higher in patients with peripheral vascular disease than in controls, and suggested that the greatest increases were associated with a poorer prognosis and disease progression[8]. Subsequent studies have confirmed an association between raised plasma fibrinogen level and peripheral arterial disease[9–11]. Raised fibrinogen levels have also been reported to predict death in patients with intermittent claudication[12,13].

Markers of fibrin turnover, FDPs such as D-dimer FDP, are also associated with peripheral vascular disease[14,15]. D-dimer FDP levels are related to disease severity in patients undergoing revascularization procedures[16], and are predictive of vascular events in patients with peripheral vascular disease[13].

Atherosclerotic lesions represent the response of arterial intima to injury, and the initiating event in the development of atheroma is endothelial disruption[17,18]. The aetiology of this endothelial disruption remains unclear, although a number of apparent 'risk factors' including hypercholesterolaemia and raised plasma homocysteine level are associated with endothelial injury[19]. Following endothelial injury, platelets adhere to the exposed subendothelium, aggregate and release their contents[20,21] including platelet-derived growth factor which, together with other growth factors, stimulates migration and proliferation of smooth muscle cells[18]. These cells lay down an intimal connective tissue matrix into which plasma-derived lipid is deposited, leading to formation of the atheromatous plaque. Widespread development and progression of these atheromatous plaques results ultimately in symptomatic peripheral arterial disease. In addition to recognition of the potential role of fibrinogen in the progression of arterial disease there has also been interest in the measurement of markers of endothelial injury in vascular disease.

Fibrinogen in the pathogenesis of vascular disease

The formation of fibrin haemostatic plugs or thrombi from its precursor, plasma fibrinogen, is a primary function of the coagulation system. Organized fibrin thrombi are found in association with atherosclerotic plaques[1] and may contribute to the progression of such plaques[2,22] with the conversion of plasma fibrinogen into fibrin taking place within plaques[23–25]. Fibrin stimulates smooth muscle cell proliferation[26], an important feature of atherosclerotic plaques, and *in vitro* studies have indicated that the adhesion of platelets to artificial surfaces increases with increasing fibrinogen concentration[27,28], as does platelet aggregability in population studies[29]. FDPs are also found within atherosclerotic plaques[24,25,30] and have mitogenic properties[25,31]. FDPs have been shown to increase the release of a number of endothelial-derived growth factors[32], and to promote reversible retraction of vascular endothelial cells[33].

Fibrinogen levels are raised in patients with peripheral arterial disease[7–11]. There may be a dynamic equilibrium between the processes of coagulation and fibrinolysis that prevents arterial occlusion in normal circumstances[34] but this equilibrium may be upset in the presence of raised plasma fibrinogen levels[35]. The increase in fibrinogen level observed in peripheral arterial disease may relate to an acute-phase response to tissue ischaemia and there is evidence that resolution of critical limb ischaemia reduces fibrinogen levels, although they remain raised compared with those in population controls[36]. However, fibrinogen levels are also raised in patients with claudication[7,11] and population studies suggest that raised plasma fibrinogen is associated with the later development of cardiovascular disease in asymptomatic subjects[37].

The increased plasma fibrinogen level in patients with arterial disease is partly related to the high prevalence of smoking in this group. The Northwick Park Heart Study[38] demonstrated a strong correlation between fibrinogen level and cigarette consumption. However, the raised levels of fibrinogen encountered in vascular disease cannot be attributed solely to smoking[5,14,38], although it may be one mechanism by which smoking exerts deleterious effects[38]. Other factors contributing to raised plasma fibrinogen levels include increasing age, diabetes mellitus, hyperlipidaemia, oral contraceptive use and leucocytosis[39,40]. A small pilot study suggested that fibrinogen levels can be reduced by the administration of drugs which inhibit white cell activation[41]. There is also a genetic influence associated with variations of up to 55 per cent in plasma fibrinogen level[42–45]. Fibrinogen may represent a common biological pathway by which a number of risk factors for vascular disease exert their influence.

Endothelial markers and vascular disease

von Willebrand factor

vWF is a large multimeric glycoprotein present in platelet alpha granules, endothelium and plasma. Synthesized by the vascular endothelium and megakaryocytes[46,47], vWF plays a significant role in platelet–vessel wall interactions and acts as a carrier for coagulation factor VIII[48]. Although endothelial cells produce vWF that binds to the subendothelium, this vWF only accounts for 40 per cent of total platelet adhesion, and normal adhesion requires the presence of additional plasma vWF[49]. Platelet adhesion is therefore mediated predominately by large multimeric forms of vWF[48], released into plasma from endothelial cells stimulated by inflammatory mediators[50]. Platelet adhesion consequently can be increased beyond normal in the presence of raised plasma vWF levels[51]. The vWF-mediated adhesion of platelets to exposed collagen in the blood vessel wall appears to be of more importance than that mediated by proteins such as fibronectin[49] because it is irreversible. This fact makes vWF the important mediator of platelet adhesion at high shear rates[49].

Several studies have demonstrated an increase in plasma vWF level in patients with peripheral vascular disease[11,14,16,52–54]. An increased concentration of vWF in arterial disease is thought to reflect endothelial damage associated with atherosclerosis, and a raised level is found in individuals with risk factors for arterial disease such as cigarette smoking[55], hypertension[56] and hypercholesterolaemia[57]. Studies into the effects of percutaneous angioplasty on vWF have confirmed that acute arterial injury induced by angioplasty results in a transient increase in vWF concentration reflecting endothelial vWF release at the time of injury[58].

Plasma vWF is an essential prerequisite for the development of occlusive thrombi at sites of arterial injury in animal studies[3,59] and the formation of occlusive thrombi in experimental arterial injury can be abolished by the use of a monoclonal antibody to vWF. Therefore vWF would appear to have a central role in the endothelial response to injury and the development of arterial thrombosis; abnormally increased levels of vWF may result in an increased tendency to intravascular thrombosis.

Plasminogen activator inhibitor and tissue plasminogen activator

Fibrinolysis is brought about by a complex enzyme cascade that generates localized proteolysis[60]. Central to this is the action of plasmin, which is converted from plasminogen by the action of tPA, and which subsequently cleaves cross-linked fibrin, with the production of cross-linked FDPs or, more specifically, D-dimer. Plasmin activity is specific for excessive fibrin deposits, as tPA is a poor activator of plasminogen in the absence of fibrin[60].

PAI is a fast-acting inhibitor of tPA found in normal plasma[61], and is released from stimulated platelets[62]. PAI rapidly complexes with tPA to reduce its activity in plasma. The binding of PAI to clot-bound tPA, however, is much slower[61]. The main role of PAI would appear to be in the regulation of plasma tPA activity.

Wide variations in PAI and tPA levels are reported in the literature[63]. Plasma levels of these substances increase with age[64], while lipid levels and dietary modification also influence tPA and PAI levels[65,66]. There is a circadian fluctuation in levels of tPA and PAI[67].

Despite this variability of plasma levels of PAI, increased PAI activity has been observed in several cardiovascular and thromboembolic diseases[63,68,69], and raised PAI levels have been found in patients with peripheral vascular disease[11,14,16,70]. Young survivors of myocardial infarction have increased levels of PAI[71], with high plasma concentrations related to reinfarction[72]. Although further investigation of the clinical role of PAI and tPA in arterial disease and revascularization surgery is required, there is a theoretical risk that a raised PAI level may lead to impairment of fibrinolysis in patients with arterial disease.

Thrombotic mediators and revascularization surgery

Graft failure occurs for many reasons, although late occlusion of both vein and synthetic grafts is often the result of progression of atheromatous disease in the native vessels[73]. Atherosclerotic changes have been reported to occur in both vein grafts[74] and synthetic grafts[75], with intramural deposition of both lipoprotein and fibrinogen-related antigens, presumably derived from the same disease processes occurring in native vessels[23]. It is likely that abnormally high levels of fibrinogen, FDP and vWF contribute to the atherosclerotic changes within grafts and native vessels that can lead to graft occlusion. The development of neointimal hyperplasia, the proliferation of smooth muscle and connective tissue in graft intima[73] which leads to vein graft stenosis, may be related to excessive fibrin deposition in patients with raised fibrinogen levels. Increased plasma fibrinogen levels were reported to be a significant risk factor for the development of vein graft stenosis in a recent study[76]. Fibrin deposition has been shown to stimulate smooth muscle cell proliferation[26,74], and there is little doubt that graft stenosis commonly results from intimal thickening due to smooth muscle proliferation[77,78].

Ultimately, however, graft occlusion is a thrombotic event and the recognized risk factors for graft occlusion, such as continued smoking and advanced disease[16,55,79], may well create a prothrombotic environment. These risk factors are known to increase plasma fibrinogen and vWF levels[16,37,55]. Adhesion of platelets to artificial surfaces increases with increasing fibrinogen concentration[27], the formation of occlusive platelet thrombi at sites of arterial injury requires vWF[3], and there is evidence of an increased thrombotic tendency in association with raised plasma vWF level[51].

In studies of the relationship between plasma fibrinogen, endothelial products and the outcome of revascularization surgery, raised plasma fibrinogen levels were associated with graft occlusion[79–82]; plasma fibrinogen levels after surgery were the strongest predictor of graft occlusion in one study of femoropopliteal vein grafts[79]. Increased FDP levels have been reported to predict failure of percutaneous angioplasty[83] and predict coronary thrombosis in patients with peripheral vascular disease[13], while increased FDP and vWF levels have both been related to adverse outcome following infrainguinal bypass grafting[82]. Many of these studies relate to late graft occlusion, although early postoperative failure may also be related to increased levels of plasma fibrinogen and other potentially thrombogenic endothelial products. It has recently been reported that preoperative determination of plasma vWF level may assist in patient selection for infrainguinal bypass grafting[82].

If altered levels of these potential thrombotic mediators are related to increased risk of heart disease, death and graft occlusion, then therapies aimed at reducing levels of plasma fibrinogen, vWF and other thrombogenic substances could improve the results of revascularization. Postoperative anticoagulation appears to improve survival, but not graft patency, following femoropopliteal bypass grafting[84]. It has therefore been suggested that determination of FDP levels may identify a high-risk group of patients who are more likely to benefit from anticoagulation[85]. The evidence that fibrinogen and vWF levels influence formation of platelet thrombi and platelet adherence[3,26,51] suggests that antiplatelet therapies may also improve the results of surgery, although a beneficial effect of such therapy was only shown after meta-analysis[86]. A recent study suggests that graft patency is more likely to be improved by the use of postoperative low molecular weight heparin[87].

Conclusion

There is now considerable evidence linking plasma fibrinogen and endothelial products to the pathogenesis of atherosclerosis. This may be of relevance both to graft occlusion following revascularization surgery, and to perioperative morbidity and mortality rates in vascular patients. A few published studies have demonstrated that high levels of potential thrombotic mediators are associated with adverse outcome, although a clear causal relationship between raised levels of plasma fibrinogen and endothelial products, and vascular disease remains to be established. Major improvements in surgical technique and graft materials are unlikely in the near future. Vascular surgeons should turn their attentions to the composition of blood in the hope that modification of the prothrombotic state found in association with advanced peripheral arterial occlusive disease will improve the results of their operative endeavours. Randomized clinical trials are required to assess the effects of currently available anticoagulant and antiplatelet therapies, both individually and in combination, on clinical outcomes following revascularization surgery, and on the relationship of potential thrombotic mediators such as plasma fibrinogen and vWF.

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Digest

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the January to March 1997 issues of *Der Chirurg*. A digest for the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal.

Reviews

Articles published in the review series in January 1997 concern diagnosis and treatment of acute appendicitis and specifically address the use of laparoscopy. The February issue reviews current aspects of endocrine surgery with particular reference to classification of gastrointestinal neuroendocrine tumours, treatment of insulinoma and management of neuroendocrine liver metastases. The March issue carries articles considering the use of minimally invasive techniques in patients with gastrointestinal tract cancer.

Inguinal hernia repair

The use of drains in elective surgery appears to be a never-ending story. The increasing use of minimally invasive techniques for hernia repair has raised new interest in measures to reduce discomfort after open hernia repair. Such discomfort may in part be due to insertion of drains into the wound area. The cost of using drains is another, more minor, issue. Finally, drains may be undesirable when the operation is to be performed as an outpatient procedure. On the other hand all of us recall patients with a large and unpleasant looking wound haematoma following hernia repair. Such haematomas may cause considerable discomfort to the patient and embarrassment to the surgeon.

The group from Aachen has a long-standing interest in hernia repair and has now addressed the need for subcutaneous drains following open hernia repair in a prospective, randomized and controlled trial[1]. Between January and October 1994 100 patients were randomized by the envelope method during operation at the end of meticulous haemostasis and before wound closure to receive a subcutaneous suction drain (Redovac; Sterimed, Püttlingen, Germany) or no drain. All hernias were repaired under local anaesthesia by the Shouldice technique. Patients were mobilized immediately after return to the ward and drains were removed after 2 days. To determine subjective symptoms patients were asked to complete a questionnaire about discomfort and pain when lying in bed, getting up, walking, straining or coughing. Patients with drains developed significantly greater volumes of wound secretions at 24 hours: mean(s.d.) 36(23) ml *versus* 3(6) ml in those without drains. After removal of the drains wound secretions were minimal in both groups (less than 5 ml/day). Using a visual analogue scale postoperative discomfort was highest in both groups on coughing, getting up and walking, and this was more pronounced in patients with a drain although the differences observed were not significant. Two patients in the drainage group developed subcutaneous abscess requiring revision and one of these presented with recurrent hernia only 4 months later. No wound abscess was reported from the group without drainage. Patients without a drain resumed household activities after 5 days and returned to work after 7 days; those with a drain resumed domestic work after 13 days and returned to work after 17 days ($P < 0{\cdot}05$). The authors conclude that drains stimulate wound secretion, which would serve to justify their insertion only in retrospect. Although a negative effect of drainage could not be demonstrated the authors recommend that use of drains after open hernia repair should be abandoned.

In another prospective, randomized and controlled trial from Bergisch-Gladbach[2] different techniques for inguinal hernia repair were compared. The authors hypothesized that tension-free inguinal hernia repair according to Lichtenstein and Amid might result in complete resolution of postoperative pain at least 2 days earlier than that observed in patients with conventional Shouldice repair. Between March 1995 and November 1995 a total of 64 patients were randomly allocated to either tension-free or Shouldice repair immediately before operation by the sealed envelope method. Operations were performed by four surgeons with longstanding experience in Shouldice repair, and only after tension-free repair was studied in the USA and in 33 local patients thus minimizing the potential effect of a learning curve on results. For this technique a polypropylene mesh (Prolene, Ethicon, Norderstedt, Germany) was used. Postoperative pain was scored by means of a visual analogue scale. Mean(s.d.) operating times were 43(10) min for the Shouldice repair and 31(8) min for tension-free repair. All patients were mobilized on the day of the operation. Six of 32 patients in the tension-free group and four of 32 patients in the Shouldice group developed postoperative haematoma, but wound infection was not observed. No significant differences between the two types of operation could be determined. All patients were pain free after the fifth postoperative day. The original hypothesis that tension-free repair would result in a higher proportion of patients achieving early freedom from pain was therefore not confirmed. The authors conclude that the Shouldice repair should be preferred since it does not require insertion of a mesh, but they concede that only long-term observation will reveal recurrence rates and this will be critical for the choice of operation.

Laparoscopic treatment of gastrointestinal malignancy

The extensive use of laparoscopic instruments is increasingly being extended to the treatment of gastrointestinal malignancy. Surgeons from Munich[3] report on the use of laparoscopy for staging gastrointestinal malignancy. In their experience extended diagnostic laparoscopy has been used particularly in patients with gastric carcinoma to determine whether potentially curative operation is possible, whether neoadjuvant chemotherapy is indicated in patients with locally advanced tumours or whether only palliative treatment should be attempted. The authors identified by means of endosonography, sonography and computed tomography (CT) 111 patients with advanced gastric cancer as candidates for diagnostic laparoscopy. Forty-two per cent of tumours were located in the proximal stomach, 45 per cent in the mid-stomach and 13 per cent in the distal stomach. Approximately 50 per cent of tumours were of the intestinal type. In 45 of 111 patients diagnostic laparoscopy resulted in a change of clinical tumour stage. In 26 patients previously unrecognized peritoneal seeding was visualized; three patients had direct infiltration of the liver and another four patients had distant metastases. In 17 patients tumours were staged down: liver metastases were excluded in ten patients, peritoneal carcinomatosis in four and infiltration of neighbouring organs in eight patients. In summary, the authors have performed a total of 450 diagnostic laparoscopies between 1988 and 1995. Six patients required conversion to open operation and only one patient died after surgery. In the authors' experience diagnostic laparoscopy is safe and this was supported by a review of the pertinent literature. They recommend diagnostic laparoscopy for staging of advanced gastric cancer when neoadjuvant therapy is being considered, but also for adenocarcinoma of the distal oesophagus and for pancreatic cancer, when exploratory laparotomy may be avoided.

Laparoscopy has also been used for treatment of intestinal cancer. In a series of 111 patients with colorectal cancer operated during a 12-month period, 22 patients had the tumour removed laparoscopically and four patients had a laparoscopically-assisted operation[4]. Contraindications for laparoscopic surgery were tumour infiltration into neighbouring organs, tumour diameter exceeding 8 cm on CT, sphincter-preserving resection of cancer of the middle and lower rectum, cardiopulmonary risk factors and pre-existing coagulopathy. Previous abdominal operations, obesity, and cancers of the right or left colic flexure or of the transverse colon were considered relative contraindications. No laparoscopic operation had to be converted to an open operation indicating appropriate selection criteria. The authors stress that all laparoscopic operations were performed with adherence to the same oncological criteria applied in conventional resections, with primary ligation of main supplying arteries and systematic lymphadenectomy. Although large and infiltrating tumours and low sphincter-preserving rectal resections were performed by conventional surgery, operating times were considerably longer in the laparoscopic group (mean(s.d.) 235(82) *versus* 173(58) min). Evaluation of pathology reports demonstrated that similar numbers of lymph nodes were examined in both groups (open mean(s.d.) 19(12) *versus* laparoscopic 17(8) lymph nodes per specimen). The authors point out that postoperative bowel movements occurred 1 day earlier in the laparoscopic group than in the conventional group, but made no further mention of recovery or hospital stay. Although complication rates were low the authors recommend that colorectal cancers should be operated laparoscopically only when they are entered into a clinical protocol or, preferably, into a randomized trial.

New technology

Patients aged 60 years or younger with malignant melanoma 1·1–2 mm in thickness may benefit from elective lymph node dissection according to the Intergroup Melanoma Trial. It is also recognized that sentinel lymph node (SLN) biopsy will reliably identify patients with metastatic disease to clinically unsuspicious regional nodes. SLN biopsy might therefore better define patients who could potentially benefit from elective lymph node dissection. The technique of identifying the sentinel node was originally based on injection of patent blue dye around the tumour or tumour scar. Demonstration of the sentinel node can be facilitated, however, by radiolymphoscintigraphy. Since 1995 Büchels and associates from Augsburg[5] have used ^{99m}Tc-labelled sulphur colloid (particle size less than 0·08 μm) to detect the sentinel node in 39 patients with malignant melanoma and a tumour thickness of greater than 1 mm. Six to 12 0·2 ml depots were injected intradermally or subcutaneously around the primary lesion or its scar. After 3–6 h scintigraphy was performed to reveal the sentinel node(s). At operation this node is localized by means of a hand-held gamma probe. If the operation is performed within 24 h no additional injection of the radiolabelled marker is necessary. A small skin incision is made over the 'hot spot' and the underlying node is removed and again checked for radioactivity before it is sent for pathological examination. Subsequent treatment decisions do not rely on frozen section analysis, but require precise pathological evaluation to ensure that micrometastatic disease is revealed by immunohistochemistry. The authors conclude that radiolabelling is superior to patent blue injection since this technique allows detection of the SLN in almost all patients. This is particularly useful in patients with melanoma of the trunk where several drainage basins and SLNs may exist. Five lymph nodes contained micrometastatic melanoma, but subsequent elective lymphadenectomy did not reveal further tumour deposits in the remaining nodes of the corresponding lymph basin. Using local anaesthesia the method can easily be applied to outpatients.

Minimally invasive endocrine surgery

Minimally invasive endocrine surgery has been applied to the adrenals for about 5 years. After demonstration of technical feasibility, centres with particular interest in this technique now report their initial series. The group from Marburg[6] reports on 28 operations in 26 patients performed for phaeochromocytoma ($n=8$), Conn's adenoma ($n=7$), incidentaloma ($n=6$), Cushing's adenoma ($n=4$), macronodular adrenal cortical hyperplasia ($n=2$) and angiomyolipoma ($n=1$). Conversion to open operation was required in seven procedures because of bleeding ($n=3$), inability to locate the tumour in adipose patients ($n=2$) and prolonged operating times ($n=2$). Mean operating time was 219 min and median postoperative hospital stay was 5 (range 3–12) days. Concern has been raised about hormonal secretion triggered by intraoperative manipulation of the adrenal glands especially when phaeochromocytoma is treated. In the present study only minor hypertension not exceeding that noted during the open procedures was recorded, but the need for sufficient pretreatment with alpha- and beta-receptor blocking agents is emphasized. The report from Mainz[7] covers 23 operations in 20 patients. In this series incidentaloma was most frequent ($n=7$), followed by peripheral Cushing's adenoma ($n=7$), Conn's adenoma ($n=3$), phaeochromocytoma ($n=2$) and central Cushing's syndrome ($n=4$). Median operating time was 180 (range 75–330) min and the median blood loss was recorded as 190 (0–400) ml. Conversion to open operation was necessary in three patients. Median postoperative hospital stay was 5 (range 2–12) days. Again no excessive hypertension was recorded at operation. With the exception of subcutaneous emphysema in two patients and pleural injury in another no serious complications were recorded, but neither report clearly states that all specimens were removed *en bloc*. Interestingly, the operating time of a historical group of 12 patients undergoing open operation was reported as 70 min with a similar blood loss of 250 (range 100–500) ml. Considerable enthusiasm is expressed for the minimally invasive approach in both reports, but it should be borne in mind that retroperitoneal open access also causes only minimal discomfort to the patient and is particularly attractive since it allows for a much quicker operation. Long-term results will reveal whether tearing the adrenal specimen during minimally invasive mobilization or removal will shed cells and cause local recurrence of tumours.

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Human immunodeficiency virus and lung cancer

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Background The association of human immunodeficiency virus (HIV) infection with lung cancer remains unclear. The presence of multiple risk factors in patients with HIV infection makes it difficult to identify a direct cause–effect relationship.

Methods A retrospective study of patients with lung cancer who were diagnosed, treated and followed at Harlem Hospital Center, New York, between January 1990 and December 1994 was performed. Eleven HIV-seropositive and 116 HIV-indeterminate patients with histologically proven lung cancer were identified. The two groups were compared with regard to age, sex, race, predisposing factors, stage of presentation, histological type of the tumours and survival.

Results HIV-infected patients with lung cancer were predominantly male smokers who were significantly younger than the control HIV-indeterminate patients with lung cancer. Although adenocarcinoma was seen more frequently in the HIV-seropositive group, the difference was not statistically significant. Survival in HIV-infected patients was shorter than that in HIV-indeterminate patients, suggesting that the cancer may be more aggressive in HIV-infected patients or that the progression of immunoincompetence in these patients may influence survival.

Conclusion A direct cause–effect relationship between lung cancer and HIV infection is difficult to establish in the presence of other risk factors, but the incidence of lung cancer may be increasing in HIV-infected men.

Several studies have shown that human immunodeficiency virus (HIV) is associated with a variety of neoplasms including Kaposi's sarcoma, B-cell lymphoma, skin and cervical carcinoma[1-5]. The high incidence of cancer in this group of patients, compared with expected cancer rates in age-matched control populations, appears to be related to immunosuppression in HIV-infected patients, which favours tumour cell escape from virus-specific T-cell surveillance. This hypothesis may parallel the finding that Epstein–Barr virus (EBV) infection in immunocompromised patients is associated with a variety of B-cell malignancies, including Burkitt's lymphoma[6] and post-transplant lymphoproliferative disorders[7,8]. The immune deficiency seen in EBV infection, which is associated with an increase in the expression of a T helper 2-type cytokine profile, which plays a central role in EBV-induced lymphoproliferative disorders, has recently been described in HIV-infected patients with lymphoma[9,10].

Of current concern is the role in oncogenesis of the emergence of other viruses that are coincidental with HIV infection. Specifically, it is unclear what role HIV infection plays in the development of cancer when found in association with EBV in lymphoma of the central nervous system, with human papillomavirus in cervical carcinoma and with the newly described Kaposi's sarcoma-associated herpesvirus-like virus.

Most recently, there has been interest in the association of lung cancer with HIV infection[11-18]. To explore further the relationship between HIV infection and the incidence of lung cancer, the authors have reviewed their experience in Harlem Hospital Center, New York, where 600 to 900 patients are treated annually for HIV infection.

Patients and methods

A retrospective study of 127 consecutive patients with biopsy-proven lung cancer who were treated during a 5-year period between January 1990 and December 1994 was carried out. Eleven of the 127 patients had serologically confirmed HIV infection, whereas the 116 subjects in the control group were not known to be HIV positive. Patients' charts and tumour registry records were reviewed with special attention to age, sex, race, presenting symptoms, associated illness, histological type and stage of cancer, cigarette smoking habit, HIV risk factors and patient survival. During this study, 2694 seropositive HIV-infected patients were treated in the hospital.

Significance for age, sex and stage of presentation was determined with Student's *t* test, and survival was analysed with Kaplan-Meier curves. Tumour classification was according to the American Joint Committee on Cancer revised clinical staging for lung cancer.

Results

Of the 11 HIV-positive patients with lung cancer (group 1) in this study, nine were men and two were women. The HIV-indeterminate control group with lung cancer (group 2) comprised 91 men (78 per cent) and 25 women (22 per cent) (*Table 1*). Although lung cancer was more common in men in both groups, there was no significant difference in the sex distribution between the two groups, where the male to female ratio was approximately 4:1. Group 1 consisted of ten African–Americans and one Hispanic person, and group 2 comprised 111 African–Americans, four Hispanics and one Caucasian. The preponderance of African–Americans in this study reflects the patient population in the authors' institution, which is located in a predominantly black community.

The HIV infection risk factors identified in ten of the 11 HIV-seropositive patients with lung cancer were intravenous drug abuse in nine patients and blood

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transfusion in one (*Table 2*). As this was a retrospective study, HIV risk factors were not available for all patients in the control group. Only ten of 116 patients had a history of intravenous drug abuse and one patient practised homosexuality (*Table 1*).

The median age of 49·7 years in group 1, compared with 62·7 years in group 2, suggests that lung cancer associated with HIV infection occurs in a younger patient population. The presenting clinical symptoms, which included cough, dyspnoea, haemoptysis, chest pain, weight loss, neck mass and seizures, were similar in the two groups. Nearly 90 per cent of patients in both groups were heavy cigarette smokers.

The histological distribution of the lung cancer (*Table 1*) revealed no significant difference between the two groups. Similarly, there was no difference in the clinical tumour stage distribution in the two patient populations (*Fig. 1*). Most patients in both groups presented with advanced disease (stages III and IV). In addition, no correlation was found between the stage of the lung cancer and the CD4 count, which ranged between 20 and 686 CD4/mm³ in HIV-infected patients with lung cancer (*Table 2*).

Of interest is the finding that five of the six patients in group 1 who were treated with radiotherapy did not receive a full course of irradiation because of acquired immune deficiency syndrome (AIDS)-related disorders such as pulmonary tuberculosis, viral hepatitis, *Pneumocystis carinii* pneumonia and brain tumours (*Table 2*). One patient received chemotherapy and four were too ill to have any treatment for lung cancer. In contrast, 45 patients in group 2 received a full course of radiotherapy, and 11 and 18 patients were treated with chemotherapy and surgical resection respectively. No patient in group 1 and only 18 of 116 in the control group underwent surgical resection, because of advanced disease at presentation.

The survival of HIV-infected patients with lung cancer

Table 1 Clinical details of patients with lung cancer and human immunodeficiency virus seropositivity or indeterminate status

	Group 1 (HIV positive)	Group 2 (HIV indeterminate)
No. of patients	11	116
Sex ratio (M:F)	9:2	91:25
Median age (years)	49·7	62·7
Race		
African–American	10	111
Hispanic	1	4
Caucasian	0	1
HIV risk factors		
Intravenous drug abuse	9	10
Blood transfusion	1	0
Male homosexuality	0	1
Histology		
Adenocarcinoma	5	41 (35)
Squamous cell carcinoma	4	37 (32)
Large cell carcinoma	1	7 (6)
Small cell carcinoma	0	9 (8)
Undifferentiated	1	17 (15)
Other	0	5 (4)

Values in parentheses are percentages. HIV, human immunodeficiency virus

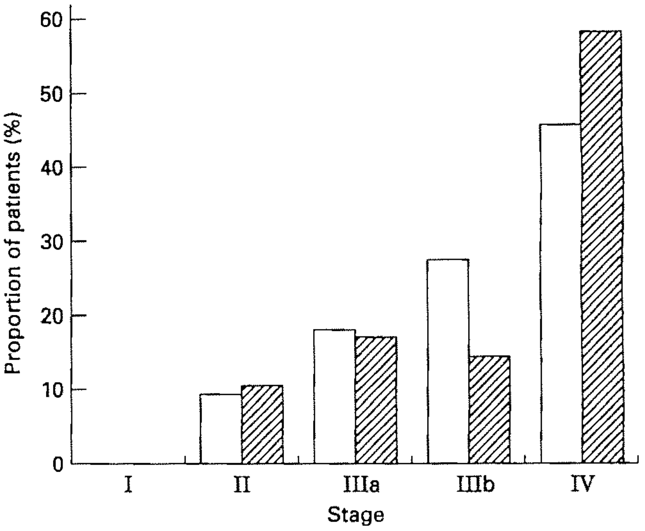

Fig. 1 Stage distribution in 11 human immunodeficiency virus (HIV)-positive patients with lung cancer (□) and in 116 of unknown HIV status (▨). Tumour classification was according to the American Joint Committee on Cancer revised clinical staging for lung cancer

Table 2 Clinical details of human immunodeficiency virus-infected patients with lung cancer

Patient no	Sex	Age (years)	CD4 count	Risk factors	Lung cancer stage	Lung cancer treatment	Associated disease	Survival (months)	Cause of death
1	M	55	344	Intravenous drug abuse	IV	Radiotherapy (18 Gy)	Viral hepatitis, toxoplasmosis	2·5	AIDS
2	F	69	167	Unknown	IV	Radiotherapy (30 Gy)	Pulmonary tuberculosis, asthma	4	AIDS
3	F	60	575	Intravenous drug abuse	IIIb	Radiotherapy (50 Gy)	Spinal cord compression, multiple metastases	2·7	Lung cancer
4	M	45	315	Intravenous drug abuse	IIIb	None	Pleural effusion, multiple metastases	3	Lung cancer
5	M	47	412	Intravenous drug abuse	IIIa	None	Viral hepatitis, PCP, pulmonary tuberculosis	3	AIDS
6	M	56	—	Blood transfusion	IV	None	Multiple liver metastases, pleural effusion	3	Lung cancer
7	M	39	57	Intravenous drug abuse	II	Chemotherapy	Brain tumour, seizures, wasting	9	AIDS
8	M	48	20	Intravenous drug abuse	IIIa	None	PCP	2	AIDS
9	M	52	286	Intravenous drug abuse	IV	Radiotherapy (12 Gy)	Brain tumours	3	AIDS
10	M	36	440	Intravenous drug abuse	IV	Radiotherapy (30 Gy)	Pharyngeal carcinoma, spinal cord compression	6	Lung cancer
11	M	40	686	Intravenous drug abuse	IIIb	Radiotherapy	PCP, pleural effusion	4	AIDS

PCP, *Pneumocystis carinii* pneumonia, AIDS, acquired immune deficiency syndrome

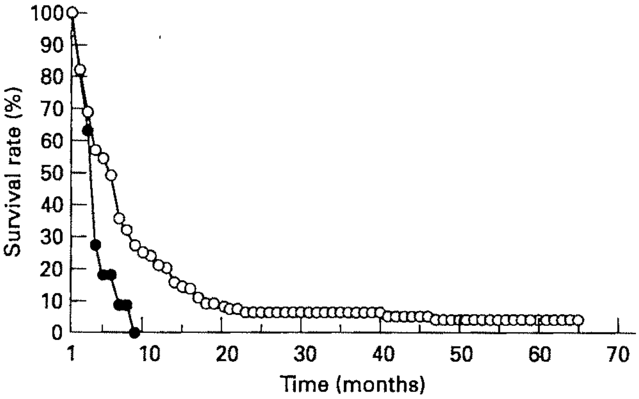

Fig. 2 Survival curve of 11 human immunodeficiency virus (HIV)-positive (●) and 116 HIV-indeterminate (○) patients with lung cancer. $P<0{\cdot}003$ between groups

was significantly shorter ($P<0{\cdot}003$) than that of HIV-indeterminate patients with lung cancer (*Fig. 2*). Only four of the 11 patients in group 1 were alive at 3 months and all patients but one were dead by 6 months; the remaining patient died at 9 months. In contrast, 82 (71 per cent) and 56 (48 per cent) of patients in group 2 were alive at 3 and 6 months respectively. Although the cause of death in seven of the 11 patients in group 1 was AIDS related, four died from complications related to advanced lung cancer. Unfortunately, because of the small number of patients in the HIV-infected group, survival cannot be compared in age-matched patients in the two groups. The relatively poor prognosis observed in patients in group 1 compared with that in group 2 might, in part, be due to the treatment received for lung cancer. Of note is the finding that the only patient in group 1 who survived for 9 months received chemotherapy.

Discussion

These data confirm earlier studies which show that lung cancer in HIV-infected patients occurs at a younger age, predominantly in men, and with a shorter median survival compared with non-HIV-infected patients with lung cancer[13,17]. This finding is not surprising as the younger population is at high risk of HIV infection as a result of its social behaviour. Adenocarcinoma of the lung is seen more frequently in HIV-infected patients with lung cancer. In contrast to previous reports[13,17], there was no difference in the present study in the male to female ratio or in the smoking habits of the HIV-infected group compared to the control group.

The use of patients whose HIV status has not been determined as controls in the present study, as well as in early studies[17], is unsatisfactory. Some patients in the HIV-indeterminate control group may well be seropositive for HIV, and this may affect the median survival of the two groups. Furthermore, the shorter median survival in HIV-infected patients with cancer raises the question of the role that progression of HIV infection plays in the early death of these patients. The present data and earlier reports[13–18] suggest that progression of this viral infection has a synergistic and/or additive effect with cancer in producing an increasing mortality rate. In addition, the shorter survival in HIV-infected patients with cancer might be influenced by the fact that such patients are not clinically fit to undergo surgical resection, adjuvant chemotherapy and/or radiotherapy.

Lung cancer may be underdiagnosed in HIV-infected patients. Concurrent chest infections, such as bacterial, mycobacterial and *Pneumocystis carinii* pneumonia, frequently encountered as complications of HIV infection, may result in the radiological misdiagnosis of lung cancer. Twenty-two per cent of HIV-positive patients with focal lung disease undergoing transthoracic needle biopsy have bronchogenic carcinoma supporting the view that lung cancer may be an under-recognized complication of HIV infection[19].

In summary, this retrospective study demonstrates that lung cancer in HIV-infected patients occurs at an earlier age and seems to behave more aggressively than in non-HIV-positive patients. The unfavourable survival seen in HIV-infected patients may, in part, be related to the progression of HIV infection to AIDS. The present findings confirm that the incidence of lung cancer may be increased in HIV-infected patients, who are generally young men. The establishment of a causative link between HIV infection and the subsequent development of lung cancer would require a multicentre study.

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Pharmacological evaluation of portal venous isolation and charcoal haemoperfusion for high-dose intra-arterial chemotherapy of the pancreas

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Background A novel system of complete portal venous isolation and charcoal haemoperfusion (PVI–CHP) has been developed in an attempt to increase dose intensity while minimizing the systemic toxicity of the cytotoxic agent during intra-arterial chemotherapy of the pancreas.

Methods Mongrel dogs were given doxorubicin (3 mg kg^{-1}), infused over a 5-min period via the splenic artery, together with PVI–CHP (group 1; $n = 5$) or without PVI–CHP (group 2; $n = 5$). Plasma doxorubicin concentrations were determined in serial samples obtained from the inlet and outlet of the CHP filter and in samples obtained from the left jugular vein (systemic levels) for up to 30 min after initiation of drug infusion. Subsequently, specimens were obtained from the pancreas, liver and heart to determine tissue doxorubicin levels.

Results The mean(s.d.) peak systemic concentration of doxorubicin in group 1 was 0·78(0·03) μg ml^{-1}, significantly lower than that in group 2 of 3·49(1·15) μg ml^{-1} ($P < 0·01$). The peak concentration of doxorubicin in group 1 was significantly lower (more than 90 per cent) than that before filtration ($P < 0·01$). Tissue doxorubicin concentration in the pancreas was similar in both groups. However, concentrations in the liver and heart were significantly lower in group 1 than in group 2 ($P < 0·05$).

Conclusion These results indicate that PVI–CHP can produce a significant reduction in systemic drug exposure and may allow dose intensification during intra-arterial chemotherapy for the pancreas.

Despite the advent of various imaging modalities, the early detection of pancreatic carcinoma is still difficult[1], and curative resection is rarely possible. Under these circumstances, to improve the prognosis, many investigators have advocated multidisciplinary approaches combining either intraoperative or postoperative irradiation and systemic chemotherapy[2–13]. Unfortunately, the outcome is usually dismal; the ineffectiveness of these approaches demonstrates that current treatment regimens are inadequate.

Recently, a number of investigators have reported enhanced tumour response with intra-arterial chemotherapy for pancreatic carcinoma[14–19]. Despite the improved response, however, gains in survival by this approach are controversial[20]. Moreover, intra-arterial chemotherapy continues to be associated with both local and systemic side-effects. In an attempt to achieve dose intensification while reducing the systemic toxicity of intra-arterial chemotherapy for pancreatic carcinoma, the authors have developed a novel system in which complete portal venous isolation (PVI) and charcoal haemoperfusion (CHP) is performed. The purpose of this study was to determine pharmacokinetically whether this novel system limits systemic exposure to doxorubicin after regional arterial infusion.

Materials and methods

Experimental model

Eleven mongrel dogs of either sex, weighing a mean(s.d.) of 12·2(2·8) kg, were used. Only one dog was excluded from the analysis because of technical failure in approaching the splenic artery. The rest were assigned to two groups: group 1, in which the animals received doxorubicin via the splenic artery, together with PVI–CHP ($n = 5$), and group 2, control animals, in which only the splenic arterial infusion of doxorubicin was performed ($n = 5$). In both groups, general anaesthesia was induced with an intravenous pentobarbital infusion (25 mg kg^{-1}), and a catheter (6 Fr) was inserted into the right jugular vein for fluid replacement. Another catheter (4 Fr) was placed in the right carotid artery to monitor blood pressure and take blood samples. Laparotomy was performed and an arterial infusion catheter (4 Fr) was placed in the proximal portion of the splenic artery, via the left gastric artery. The short gastric arteries were divided to prevent drug perfusion to the stomach. Heparin (100 units kg^{-1}) was given intravenously in both groups before administration of doxorubicin.

For the establishment of PVI–CHP, a catheter (12 Fr) was placed in the portal vein, via the splenic vein, to capture portal venous blood (group 1). A return catheter was placed in the left jugular vein (*Fig. 1*). These two catheters were connected to an extracorporeal system consisting of a centrifugal pump (Bio-pump; Biomedicus, Minneapolis, Minnesota, USA) and a CHP filter (DHP-1; Kuraray, Osaka, Japan). The circuit was primed with 200 ml physiological saline. Immediately before the establishment of PVI–CHP, heparin was administered intravenously to obtain anticoagulation. Bypass was then initiated once the portal vein had been clamped at the porta hepatis with a vascular clamp. Isolated portal venous blood, directed to the CHP filter by the centrifugal pump, then returned to the left jugular vein. The PVI–CHP was maintained for 20 min from the initiation of doxorubicin infusion. Blood flow rate through the extracorporeal circuit was monitored by an electromagnetic flowmeter (DP-38P; Biomedicus)

Intra-arterial infusion of doxorubicin

In both groups, doxorubicin (3 mg per kg body-weight) (Adriamycin; Kyowahakko, Osaka, Japan) was dissolved in 10 ml physiological saline and administered continuously over a 5-min period into the splenic artery via a pump injector (STC-521 syringe pump; Terumo, Tokyo, Japan).

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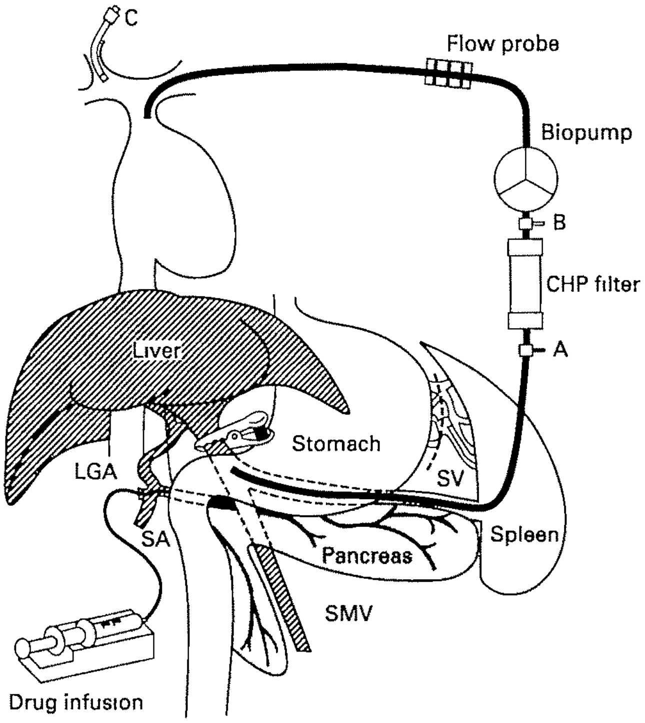

Fig. 1 Schematic representation of intra-arterial chemotherapy of the pancreas with portal venous isolation and extracorporeal charcoal haemoperfusion (CHP) The short gastric arteries were divided. An arterial infusion catheter was placed in the proximal portion of the splenic artery via the left gastric artery. A, B and C, blood-sampling points; ----, clamping site. SV, splenic vein, SA, splenic artery; SMV, superior mesenteric vein; LGA, left gastric artery

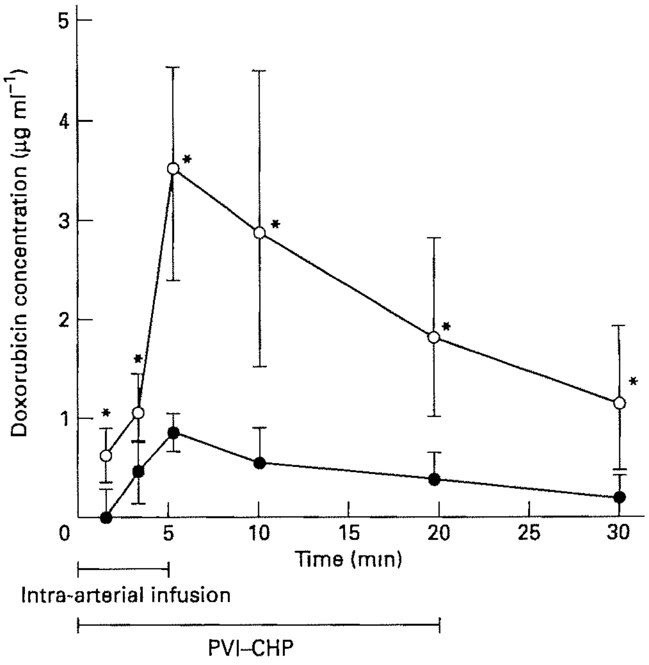

Fig. 2 Plasma doxorubicin concentration in systemic blood Values are mean (s.d.). ●, Group 1 (portal venous isolation and charcoal haemoperfusion (PVI-CHP)); ○, group 2 (control). *$P < 0\cdot 01$ (Student's t test)

Pharmacokinetic evaluation

Serial blood samples were obtained from the right carotid artery (for systemic determination) for up to 30 min after initiation of drug infusion. In addition, in group 1, blood samples were obtained from the inlet and outlet side of the CHP filter. In both groups, animals were killed 30 min after the initiation of drug infusion, and specimens were obtained from the pancreas, liver and heart to determine tissue doxorubicin concentrations. Plasma and tissue doxorubicin levels were determined by high-performance liquid chromatography, as described elsewhere[21]. The doxorubicin extraction ratio achieved by the CHP filter was calculated by the formula:

$$\text{Extraction ratio (\%)} = C_i - C_i'/C_i \times 100$$

The amount of drug removed during 20 min of PVI–CHP was calculated; the proportion of the administered dose, defined as the clearance fraction, was calculated by the equation·

$$\text{Clearance fraction (\%)} = \Sigma((C_i + C_j)/2 - (C_i' + C_j')/2)$$

$$\times Q_{ij} \times T_{ij}/\text{Amount of drug administered} \times 100$$

where C_i is the inlet concentration (μg ml^{-1}) at sampling time i, C_j is the inlet concentration at sampling time j, C_j' is the outlet concentration at sampling time i, C_j' is the outlet concentration (μg ml^{-1}) at sampling time j, Q_{ij} is the average blood flow rate (ml min^{-1}) between sampling times i and j, T_{ij} is the time (min) between i and j, and j is the sampling time immediately after sampling time i.

Student's t test was used for statistical analysis $P < 0\cdot05$ was considered significant. Values are mean(s.d.), unless stated otherwise.

Results

Time course of plasma doxorubicin concentrations

Plasma doxorubicin concentrations in systemic and portal venous blood are shown in *Figs 2* and *3* respectively. In group 1, systemic doxorubicin levels reached the peak value 5 min after the initiation of drug infusion, but decreased rapidly over 30 min. In group 2, systemic doxorubicin concentrations reached the peak value at 5 min and decreased thereafter, but remained relatively high, even after 30 min. The systemic doxorubicin level in group 1 was significantly lower than that in group 2 ($P < 0\cdot01$) at all time points measured during the 30 min after drug infusion. The area under the time–concentration curve (AUC) for systemic blood was 8·5 μg min ml^{-1} in group 1 and 58·9 μg min ml^{-1} in group 2 ($P < 0\cdot01$). In group 1, the plasma doxorubicin concentration of portal venous blood at the inlet side of the CHP reached a peak value (14·74(1·67) μg min ml^{-1}) 1 min after the initiation of drug infusion. At the outlet side of the CHP, plasma doxorubicin concentration reached a peak value (1·29(0·07) μg min ml^{-1}) 5 min after initiation of infusion. Until 10 min during PVI-CHP plasma doxorubicin levels at the outlet side of the CHP were significantly lower than those at the inlet side ($P < 0\cdot01$), indicating substantial drug extraction by the CHP filter.

Doxorubicin extraction by the filter and drug clearance fraction

Fig. 4 shows the time course of the extraction of doxorubicin with the CHP filter, expressed as the extraction ratio. The drug extraction ratio was 80 per cent or higher at all time points measured during drug infusion. After the end of the infusion, the extraction ratio

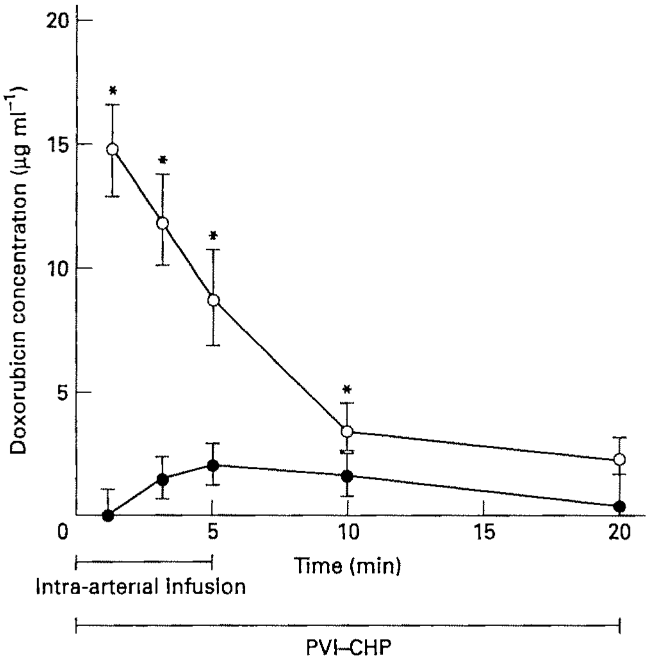

Fig. 3 Plasma doxorubicin concentration at the inlet and outlet side of the charcoal haemoperfusion filter. Values are mean(s.d.) ○, Inlet concentration; ●, outlet concentration. PVI-CHP, portal venous isolation and charcoal haemoperfusion. $^{*}P < 0{\cdot}01$ (Student's t test)

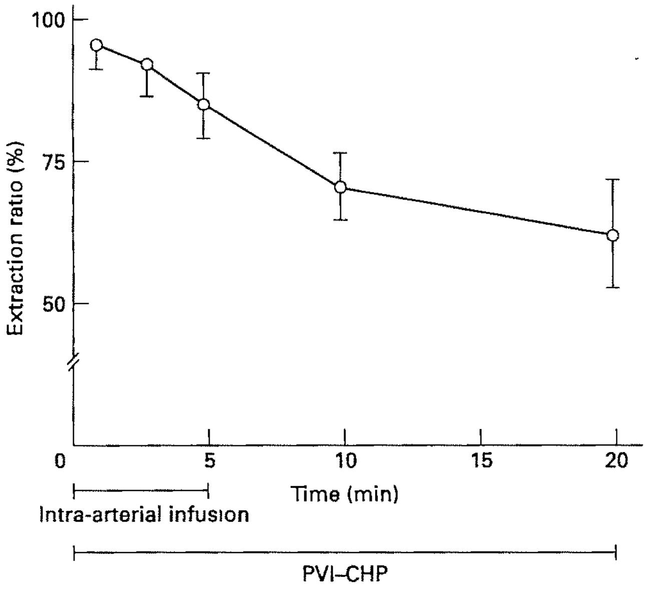

Fig. 4 Doxorubicin extraction ratio by the charcoal haemoperfusion filter. Values are mean(s.d.). PVI-CHP, portal venous isolation and charcoal haemoperfusion

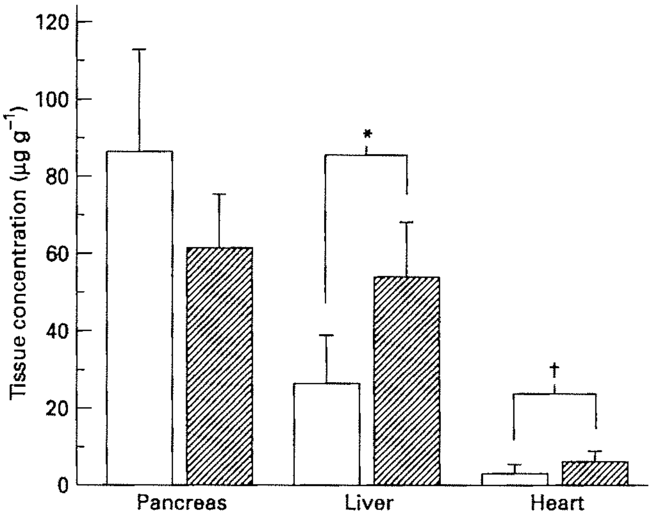

Fig. 5 Tissue doxorubicin concentration in the pancreas, liver and heart. Values are mean(s.d.). □, Group 1 (portal venous isolation and charcoal haemoperfusion); ▨, group 2 (control). $^{*}P < 0{\cdot}05$, $^{\dagger}P < 0{\cdot}01$ (Student's t test)

decreased gradually, being 61·3(10·2) per cent at 20 min. The mean(s.d.) drug clearance fraction with the PVI–CHP was 27·9(3·6) per cent.

Tissue doxorubicin concentrations

The mean tissue doxorubicin concentration in the pancreas was slightly higher in group 1 than in group 2 animals; the difference was not significant (*Fig. 5*). In contrast, the mean tissue doxorubicin concentration in the liver was significantly lower in group 1 than in group 2 ($P<0{\cdot}05$), the values being 27·35(9·15) and 52·37(18·51) μg g^{-1} respectively. In the heart, mean values were 1·77(0·88) and 4·91(0·62) μg g^{-1} respectively in groups 1 and 2 ($P<0{\cdot}01$).

Discussion

The indications for surgical resection of pancreatic carcinoma are limited, because most patients are in an advanced stage at the time of diagnosis[1]. Thus, efforts have been directed towards multidisciplinary therapies combining systemic chemotherapy with intraoperative and postoperative irradiation therapy[2–13]. However, the results of these therapeutic approaches are disappointing. One possible explanation for the ineffectiveness of systemic chemotherapy lies in the hypovascular nature of pancreatic carcinoma; regional drug delivery is limited in such hypovascular tumours[22].

Considering these shortcomings of systemic chemotherapy for pancreatic carcinoma, a number of investigators have employed intra-arterial chemotherapy to improve tumour response, increasing local concentrations of chemotherapeutic agents[14–20]. Kunimura *et al.*[22] demonstrated histologically the increased tumoricidal effect of this approach in comparison with systemic chemotherapy. Ishikawa *et al.*[15] infused angiotensin II with standard doses of intra-arterial doxorubicin and methotrexate to increase drug delivery to the tumour tissue, and reported an improved tumour response rate, measured by tumour shrinkage and by decreased levels of tumour markers. McCracken *et al.*[18] reported that a combination of intra-arterial chemotherapy and radiation therapy produced a good tumour response in 44 per cent of patients with pancreatic carcinoma. Despite the improved tumour response, however, survival gains in these trials are somewhat modest and long-term survival is unusual. It can be postulated that the dose is not yet high enough to demonstrate a clear difference in outcome.

To allow dose intensification, while reducing systemic exposure following regional infusion of chemotherapeutic agents, drug extraction with membrane or charcoal filters, together with non-isolated venous drainage, has been reported by a number of investigators[23-25]. However, these attempts were unsuccessful, no doubt because the venous drainage of the target organ was not isolated completely; the profound systemic distribution of the drugs takes place before elimination. Arredondo *et al.*[16] recently reported an experimental model of haemodynamic isolation of the pancreas and perfusion with chemotherapeutic agents in dogs. The perfusion circuit was constructed by cannulating the superior pancreaticoduodenal artery and vein, and dividing all other vessels that enter and leave the pancreas and duodenum. However, it is obvious that complete haemodynamic isolation–perfusion of the pancreas is extremely difficult in the clinical setting because of the many inflow and outflow vessels and frequent cancer invasion to these vessels. Furthermore, in general, the isolation–perfusion model is very complicated.

A novel system combining complete venous isolation and charcoal haemoperfusion for the intra-arterial chemotherapy of a tumour-bearing organ was first described by investigators at this institution[26]. Initial studies in an animal model clearly demonstrated the feasibility and efficacy of hepatic venous isolation and charcoal haemoperfusion (HVI–CHP) for the elimination of chemotherapeutic agents with good charcoal affinity following regional infusion. Subsequently, a phase I study was conducted in patients with malignant liver tumours, beginning in May 1989[27]. These clinical studies have confirmed that HVI–CHP allows major increases in dosage levels, while reducing systemic exposure. To extend this treatment concept to the pancreas, the present study was undertaken to determine whether PVI–CHP would also limit systemic exposure to chemotherapeutic agents after intra-arterial infusion.

In this study, it was decided to employ doxorubicin because it is a potent cytotoxic agent with a dose-dependent action, and has also been used to treat pancreatic cancer[8,10,15]. Although other standard agents, such as 5-fluorouracil or ifosfamide, would seem to be better initial candidates for investigation, doxorubicin was chosen because it has well documented pharmacokinetic data for HVI–CHP[26]. In addition, pharmacokinetic data for PVI–CHP with doxorubicin can be extrapolated to 5-fluorouracil, as the two drugs exhibit a similar extraction ratio with the CHP filter[28].

The present authors and others have postulated previously that drugs such as doxorubicin, with a low hepatic extraction ratio, are ideally suited to maximize the pharmacological advantages of HVI–CHP[27,29]. As shown by the drug clearance fraction, PVI–CHP eliminated approximately 28 per cent of the drug administered. Throughout the experiments, systemic concentrations of doxorubicin were always significantly lower in animals with PVI–CHP than in controls, by a factor of 3·0–14·1. Furthermore, PVI–CHP achieved an 86 per cent reduction in systemic exposure to doxorubicin, as assessed by estimating the AUC. These pharmacokinetic findings for doxorubicin with PVI–CHP were almost accordant with the experimental and clinical results obtained with HVI–CHP[26,27], suggesting that doxorubicin undergoes first-pass extraction in the pancreas at a rate similar to that in the liver, when administered by regional arterial infusion.

It could be possible to extend the application of this system to other cancer-bearing organs such as the kidney and pelvis, because of the ease of performing venous isolation. The authors recently tested whether infrarenal inferior vena caval isolation and charcoal haemoperfusion combined with internal iliac arterial infusion could increase pelvic delivery of doxorubicin with reduced systemic drug exposure in a canine model. Systemic exposure to doxorubicin, as assessed by the AUC, was reduced 3·7-fold by this method compared with controls (unpublished data). Taken together, these findings indicate that this system may be applicable to other drugs poorly extracted by the target site and in other clinical and anatomical situations in which vascular isolation can be accomplished.

The charcoal filter in this system achieves the equivalent of a pharmacological first-pass effect by binding drug that is not extracted by the infused region. Patient data with HVI–CHP[27] showed that the filter extraction ratio of doxorubicin averaged 91 per cent during drug infusion at a dose ranging from 100 to 150 mg m^{-2}. Other investigators also tested three different doses of doxorubicin (1, 3 and 9 mg kg^{-1}) in a pig model of HVI–CHP, and reported that the extraction ratio was over 86 per cent irrespective of drug dose during infusion[29,30]. Therefore, the CHP filter appears to cope with dose intensification of doxorubicin up to 9 mg kg^{-1}. However, for clinical use of PVI–CHP, the maximum dose should be carefully determined in a stepwise manner depending on local and systemic tolerance to high-dose drug infusion.

Animals in group 1 showed a slightly higher level of doxorubicin in the pancreas than those in group 2. Blood flow rates of the portal vein in group 1 animals ranged from 100 to 320 ml min^{-1} during PVI–CHP, and were apparently lower than the rates under physiological conditions. This finding suggests that the pancreas became congested during PVI–CHP, resulting in increased tissue extraction of doxorubicin in this organ. Tissue doxorubicin concentrations in the liver and heart, on the other hand, were both significantly lower in group 1 than in group 2, indicating again that systemic exposure to doxorubicin was profoundly reduced by PVI–CHP. These results, taken together, indicate that, with PVI–CHP, significant dose intensification of doxorubicin may be achieved for intra-arterial chemotherapy of the pancreas.

With regard to the route of drug administration, the splenic artery and/or gastroduodenal artery have generally been used in previous studies[14-20]. As the response of pancreatic cancer to the treatment is beyond the scope of this study, splenic arterial infusion was tested to simplify the experimental model. However, advanced pancreatic cancer frequently involves the entire pancreas and its surrounding tissues, so more extensive arterial infusion, including other tumour-supplying arteries, may be required in the clinical setting. Apart from a number of the tumour-supplying arteries, the majority of drainage veins eventually enter the portal vein. Therefore, it is reasonable to speculate that PVI–CHP would also be effective in eliminating drugs given via regional arteries, such as the gastroduodenal artery, in addition to the splenic artery.

Local toxicity of the drug still remains a major dose-limiting factor for PVI–CHP. Arredondo *et al.*[16] reported that an appropriate dose of mitomycin C for the haemodynamic isolation and perfusion of the pancreas was 0·25 mg kg^{-1}, as they noted both acute and chronic pancreatitis and duodenal ulceration or perforation at a dose of 0·5 mg kg^{-1}. It is likely that, in the majority of patients with advanced disease, pancreatic tissue is replaced by carcinoma. Thus, local drug toxicity in the pancreas may be less serious in humans than in the animal model with an intact pancreas. Regarding duodenal drug toxicity, however, it is recommended that, for the clinical application of PVI–CHP, a clamping device be placed on the duodenum during drug infusion.

In summary, the novel system of PVI–CHP described here may allow dose intensification of chemotherapeutic agents with good charcoal affinity during intra-arterial chemotherapy for the pancreas. In patients with irresectable pancreatic carcinoma, the relative simplicity of this approach could facilitate the use of high-dose regional chemotherapy.

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Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin

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Background Liver resection for metastatic colorectal cancer has been established. Nevertheless, it is still controversial whether the surgical margin from the tumour edge to the cut surface of the liver is a significant prognostic factor in hepatic resection for colorectal metastatic liver cancer.

Methods To clarify the prognostic risk factors in hepatic resection for colorectal metastasis, univariate and multivariate analyses were performed. Between April 1985 and April 1995, 31 patients underwent curative hepatic resection for metastatic colorectal cancer. The clinical and pathological factors were examined retrospectively.

Results Overall 1-, 3- and 5-year survival rates of the patients were 92, 42 and 39 per cent respectively. Pathological study of 16 resected specimens with a solitary liver tumour revealed hepatic vein invasion by cancer cells in two of 16 cases, portal vein invasion in three, microsatellite lesions in two and biliary tract invasion in six cases. In resected specimens with a solitary tumour measuring less than 4 cm in diameter, one of these factors was observed in only two of nine cases, whereas in specimens with a solitary tumour measuring more than 4 cm in diameter, these factors were observed in six of seven patients ($P < 0{\cdot}05$). The distance from the tumour edge to the intrahepatic invasion was less than 10 mm. With univariate analysis, tumour size of 4 cm or more in diameter, an interval of 6 months or less between colorectal and hepatic resection, four or more gross tumours, bilobar involvement and a resection margin from the tumour of less than 10 mm were found to be significant factors indicating a poor prognosis. Cox's proportional hazards model identified a tumour of 4 cm or more in diameter and a resection margin from the tumour of less than 10 mm as poor prognostic factors ($P < 0{\cdot}05$).

Conclusion In treating metastatic colorectal cancer to the liver, the surgical margin should be more than 10 mm because occult intrahepatic invasion was always found to be located within 10 mm from the edge of the tumour.

The effectiveness of liver resection for metastatic colorectal cancer is well established[1–3]. In addition, many reports on prognostic factors in patients with metastatic colorectal cancer who undergo hepatic resection have been published[1–10]. Nevertheless, it is still controversial as to whether or not the surgical margin from the tumour edge to the cut surface of the liver is a significant prognostic factor in hepatic resection for colorectal metastatic liver cancer. Several reports[2,3,7] have shown that this surgical margin should be more than 10 mm. On the other hand, other reports[8–10] have stated that the surgical margin is not a significant risk factor. Even in the reports in which the margin was found to be a significant risk factor for survival after hepatic resection, the reason why a surgical margin of 10 mm should be a significant prognostic factor has not been clarified.

In this study, an attempt was made to identify the prognostic factors in resection of colorectal metastases to the liver, paying special attention to both microscopic intrahepatic invasion and the surgical margin.

Patients and methods

Between April 1985 and April 1995, 31 patients underwent hepatic resection for metastatic colorectal carcinoma. These were all attempts at curative resection with no residual tumour. The 17 men and 14 women ranged in age from 41 to 78 (mean 65) years.

A retrospective review of all available clinical records of the patients was conducted. Follow-up and patient outcome were documented by clinical visits, telephone interview or correspondence.

Pathological study of resected specimens was also performed. Resected specimens were cut along the largest diameter and then fixed with formalin. The entire cut surface was sectioned from the slice with the largest diameter and then embedded in paraffin. Microscopic sections were stained with haematoxylin and eosin.

In resected specimens with solitary tumours ($n = 16$), the incidence of microscopic intrahepatic invasion, such as portal vein invasion by cancer cells, microsatellite lesions, hepatic venous invasion and bile duct invasion, was determined. In specimens with intrahepatic invasion, the distance from the tumour edge to the intrahepatic invasion was measured.

According to the minimum width of the surgical margin in the freshly resected specimen, the surgical margin was determined. When the margin was less than 10 mm, the specimen was defined as tumour margin positive; when a surgical margin equal to or more than 10 mm was left, it was defined as tumour margin negative.

The following clinical and pathological risk factors were examined for prognostic influence: sex, age, interval

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between primary colorectal resection and hepatic resection, preoperative serum levels of carcinoembryonic antigen (CEA) and CA19-9, number of metastatic sites, distribution of the tumour in the liver, the largest metastatic nodule diameter, histological differentiation of the secondary tumour, microsatellite lesions, and intrahepatic invasion of the portal vein, hepatic vein and bile duct.

Statistical analysis

The χ^2 test was used to assess the incidence of intrahepatic invasion. Survival time was calculated from the date of hepatic resection until death. Survival curves were generalized using the Kaplan–Meier method and were then compared with the log rank test. A univariate Cox proportional hazards model was used to calculate the relative risk of mortality and 95 per cent confidence intervals. The BMDPP2L program (BMDP, Los Angeles, California, USA) was used for multivariate adjustment of all co-variates, using a step-wise regression analysis on an IBM 4831 computer. $P < 0\cdot05$ was considered statistically significant.

Results

The overall survival rate was 92 per cent at 1 year, 42 per cent at 3 years and 39 per cent at 5 years (*Fig. 1*).

Intrahepatic invasion of cancer cells

Microscopic intrahepatic invasion is shown in *Fig. 2*. In 16 patients with solitary tumours, portal vein invasion by cancer cells was observed in three cases, microsatellite lesions in two, hepatic venous invasion in two, and bile duct invasion in six. In resected specimens with a solitary tumour measuring less than 4 cm in diameter, only two of nine cases showed any of these factors. However, in resected specimens with a solitary tumour measuring more than 4 cm in diameter, these pathological factors were observed in six of seven patients ($P < 0\cdot05$). The distance from the tumour edge to the area of microscopic intrahepatic invasion is shown in *Fig. 3*. All distances of observed intrahepatic invasion were within 10 mm.

Univariate analysis: clinical risk factors

Actuarial overall survival rates are shown in *Table 1*. Neither sex, age, level of CEA or CA19-9 nor the site of the primary tumour was a significant risk factor for survival. However, patients with less than a 6-month interval between colorectal and hepatic resection experienced a poorer outcome ($P = 0\cdot01$). Surgical margin was also found to be a significant risk factor ($P = 0\cdot04$).

Univariate analysis: pathological and operative risk factors

Actuarial overall survival rates are shown in *Table 2*. The number of metastases, the size of the tumour and tumour distribution were found to be significant risk factors for survival. Portal vein invasion, microsatellite lesion, hepatic venous invasion and bile duct invasion were not significant risk factors.

Multivariate analysis

The results of the multivariate analysis are shown in *Table 3*. Tumour size of 4 cm or more in diameter

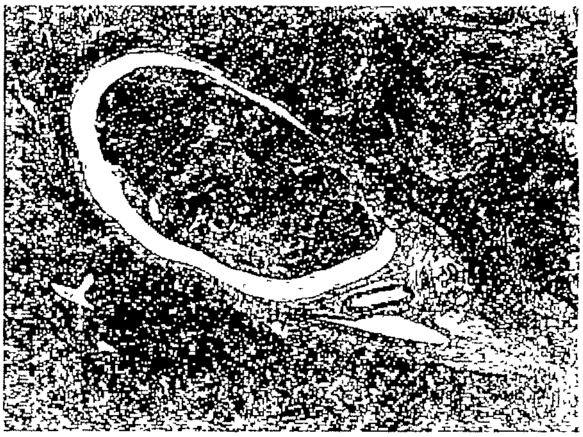

Fig. 2 Microphotograph of bile duct invasion (haematoxylin and eosin stain; original magnification ×13)

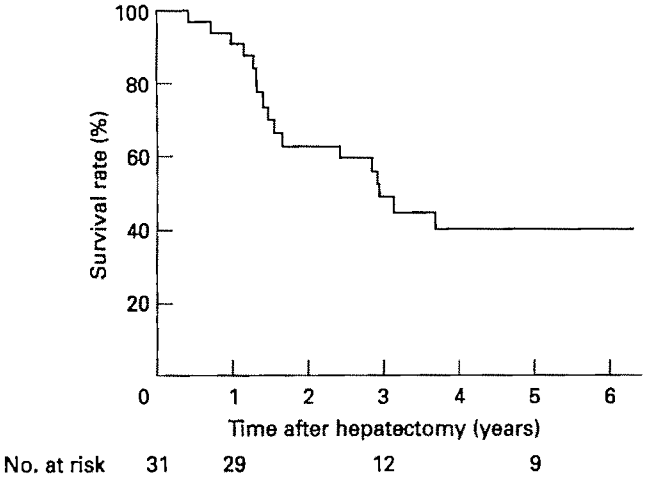

Fig. 1 Overall survival in 31 patients having hepatic resection for metastatic colorectal cancer

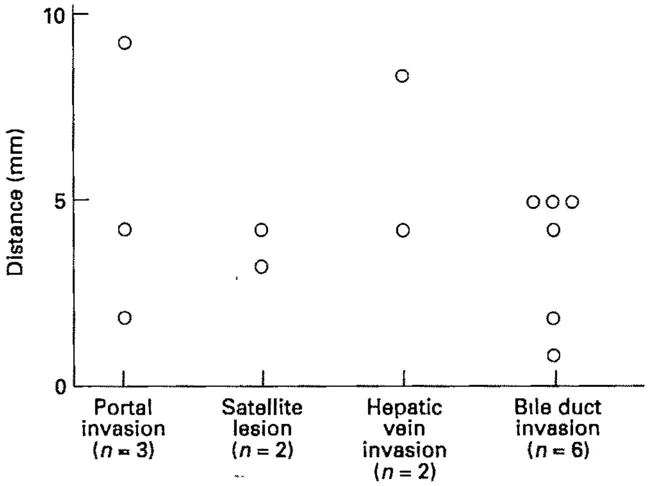

Fig. 3 Distance from the main hepatic tumour to the area of microscopic intrahepatic invasion

Table 1 Possible clinical risk factors for survival

Variable	No. of patients	Overall survival rate (%) 1 year	3 years	5 years	P†
Sex					
M	17	100	59	47	0·25
F	14	91	30	22	
Age (years)					
<60	14	93	59	48	0·25
≥60	17	100	38	28	
Disease-free interval (months)					
0–6	10	89	21	8	0·01
≥7	21	100	61	55	
CEA level (ng/ml)					
<5	12	100	81	50	0·24
≥5	19	94	40	32	
CA19-9 level (ng/ml)					
<50	10	100	58	58	0·88
≥50	10	100	54	54	
Surgical procedure*					
Minor resection	22	100	70	50	0·49
Major resection	9	95	46	22	
Surgical margin <10 mm					
Positive	10	88	31	28	0·04
Negative	21	100	71	71	

CEA, carcinoembryonic antigen. *Major hepatic resection included segmentectomy, lobectomy and trisegmentectomy; minor resection included wedge resection and sub-segmentectomy. †Log rank test

Table 2 Possible pathological risk factors for survival

Variable	No. of patients	Overall survival rate (%) 1 year	3 years	5 years	P*
No. of metastases					
Three or less	15	100	85	55	0·005
Four or more	16	86	19	19	
Tumour size (cm)					
<4	16	100	84	78	0·006
≥4	15	85	32	12	
Tumour distribution					
Unilobular	21	100	62	52	0·01
Bilobular	10	90	38	11	
Differentiation					
Well	10	100	58	28	0·40
Moderate	21	76	58	43	
Portal invasion					
Yes	10	88	28	22	0·18
No	21	100	55	48	
Satellite lesion					
Yes	8	88	32	22	0·09
No	23	100	74	50	
Hepatic vein invasion					
Yes	6	100	32	32	0·35
No	25	95	69	48	
Bile duct invasion					
Yes	9	94	58	58	0·52
No	22	100	60	38	

*Log rank test

($P = 0·015$) and a positive surgical margin ($P = 0·034$) were both found to be significant risk factors for poor prognosis.

Table 3 Results of multivariate analysis

Variable	Regression coefficient	Standard error	Relative risk	P
Tumour size	1·293	0·554	3·642	0·015
Surgical margin	1·392	0·766	2·150	0·034

Discussion

In this study, the significant risk factors for a poor outcome in multivariate analysis were (1) tumour size more than 4 cm in diameter and (2) a surgical margin from the tumour edge to the cut surface of the liver of less than 10 mm. These observations are not surprising. The incidence of intrahepatic invasion was observed to be high in the present study, especially in resected specimens with a tumour measuring more than 4 cm in diameter.

Several studies have also reported reduced survival rates and increased recurrence after resection of metastatic tumours when the surgical margin was less than 10 mm, although the ultimate mechanism for this remains to be elucidated[2,3,7].

The present study demonstrated a high incidence of microscopic intrahepatic invasion in colorectal liver metastases. In particular, even in resected specimens with solitary tumours measuring 4 cm or more in diameter, most tumours were accompanied by intrahepatic invasion. Based on these findings, intrahepatic invasion thus seems to be a satellite lesion of the metastatic tumours, and not a metastasis from the primary colonic cancer.

In the present study, the distance from the occult intrahepatic invasion to the tumour edge was examined. Recently, Yamamoto *et al.*[8] measured the distance from the tumour to the tip of the macroscopic invasion and found that it was usually more than 10 mm; therefore, a non-anatomical limited hepatic resection was justified. Nevertheless, occult invasion that cannot be detected macroscopically is considered to be more important than macroscopic invasion in the curability of the tumour, because both preoperative and intraoperative diagnosis can be made in advance[11–13]. Thus, in the present study, the distance from the tumour to the area of occult invasion, which was detected only microscopically, was measured. As a result, the distance from occult invasion to the tumour edge was within 10 mm, and suggested the surgical margin to be a significant prognostic factor.

Among the various types of intrahepatic invasion, intrabiliary invasion of cancer cells is the most common. Recently, Yamamoto *et al.*[14] reported a patient with a recurrent liver tumour with intrabiliary ductal growth after hepatectomy for metastatic rectal cancer. Nevertheless, intrabiliary recurrence has been reported to be rare[15–17] and bile duct invasion was not a significant risk factor for survival in the present study. The reason for this discrepancy, however, remains unknown.

In previous reports, adjuvant therapy was found to be effective in preventing recurrence after hepatic resection for colorectal metastatic liver cancer[18–20]. Therefore, wide resection is recommended for tumours measuring 4 cm or more in diameter and adjuvant therapy may also be useful for such patients.

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Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases

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Background The indication for surgical resection of colorectal liver metastases should be guided by technical feasibility and expected prognostic benefit. The aim of the present study was to analyse the frequency and prognostic significance of lymph node involvement of the hepatoduodenal ligament in the resection of colorectal liver metastases.

Methods A series of 126 prospectively documented patients who underwent hepatectomy for metastases of colorectal carcinoma was analysed. The prognostic factors of patients with complete resection (R_0) of the metastases were studied by multivariate analysis.

Results R_0 resection was achieved in 94 per cent. The 30-day mortality rate was 2 per cent. In all patients, lymph nodes were excised from the hepatoduodenal ligament, and histological evaluation demonstrated tumour infiltration in 28 per cent of the patients. Multivariate analysis revealed nodal involvement of the hepatoduodenal ligament ($P < 0{\cdot}0001$) and synchronous or metachronous appearance of liver metastases ($P < 0{\cdot}005$) as independent prognostic factors. The 3- and 5-year survival rates were 3 and 0 per cent for lymph node-positive patients compared with 48 and 22 per cent respectively for the node-negative group.

Conclusion Infiltration of lymph nodes in the hepatoduodenal ligament is the most important prognostic factor following R_0 resection of colorectal liver metastases.

As nearly half of all patients with colorectal cancer develop liver metastases in the course of the disease, the decision concerning the value of hepatectomy for metastasis is part of everyday clinical practice[1,2]. The indication for surgical resection of colorectal metastasis is guided not only by the technical feasibility of the procedure but also by the expected prognostic benefit in defined subgroups of patients. Various determinants of prognosis have been published[3–9]. The regional lymph nodes at the hepatic hilum have been examined systematically in only a small number of studies, and even more rarely has a multivariate evaluation of the prognostic significance of their involvement been performed[10–13]. The aims of the present study of patients with resection of colorectal liver metastasis were (1) to assess the frequency of regional lymph node involvement in metastases of the liver and (2) to determine the most important prognostic factors by specific consideration of the nodal status of the hepatoduodenal ligament using univariate and multivariate analysis.

Patients and methods

From November 1987 to December 1994, 126 consecutive patients with resection of hepatic metastases from colorectal cancer were documented prospectively The colonic or rectal carcinomas had been resected between 1982 and 1994, and in all cases complete removal (R_0 resection) of the primary tumour in the colorectum together with an adequate lymphadenectomy had been achieved[14]. Before hepatectomy for metastases, any extrahepatic tumour manifestations had been ruled out by colonoscopy, chest radiography, ultrasonography, computed tomography (CT) and in some cases bone scintigraphy. Number and site of liver metastases were very exactly defined by contrast CT and ultrasonography. Enlarged regional lymph nodes in the hepatic hilum (1 cm or bigger) were found before operation by CT in nine patients (7 per cent); six of these showed histological infiltration after operation. Enlarged hilar lymph nodes were not included in the preoperative definition of extrahepatic tumour. In all of the 126 patients, lymph nodes from the hepatoduodenal ligament were excised and examined histologically. In the same time period an additional 23 patients were operated on without removal of lymph nodes from the hepatoduodenal ligament; in some cases this was because of adhesions from previous surgical approaches (e.g. cholecystectomy) and in others because of neglect. According to macroscopic evaluation in these patients, the lymph nodes of the hepatoduodenal ligament were not infiltrated. Because the prognostic significance of hilar lymph node involvement of the liver was the main objective of this study, only the 126 patients with definite lymph node histology of the hepatoduodenal ligament were included in the analysis. Nevertheless, this group of patients did not differ significantly from the total group of 149 patients operated on with respect to all demographic or tumour-specific variables listed in *Table 1*.

Over half of the patients had one liver metastasis. Of the remainder most had two, but 11 (9 per cent) had three, five (4 per cent) had four and one patient had six metastases. By definition, metachronous metastases ($n = 67$) were those that evolved more than 6 months after operation for the primary colorectal tumour. If synchronous metastases ($n = 59$) were present, the choice of simultaneous or two-stage removal was based on the size of the metastasis in conjunction with the extent of hepatectomy, the expected stress of the colorectal tumour operation and the patient's general risk. Generally, small metastases that were easy to resect were removed simultaneously, while large metastases that required technically demanding resections were removed after adequate recovery from the colorectal surgery, especially when the patient was at increased risk.

The surgical technique of hepatectomy for liver metastases included intraoperative ultrasonography, partial vascular exclusion with the help of Pringle's manoeuvre, ultrasonic dissection of liver parenchyma and lymphadenectomy of the hepatoduodenal ligament. Intraoperative ultrasonography by one

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Table 1 Demographic and tumour-specific parameters of 126 patients who had resection of colorectal liver metastases with histological examination of lymph nodes from the hepatoduodenal ligament

Patient characteristics	
Median age (years)	61 (38–80)*
Patients aged >65 years	45 (36)
Sex ratio (M:F)	77:49
Colonic carcinoma	
pT category	
pT_2	51 (41)
pT_3	67 (53)
pT_4	8 (6)
pN category	
pN_0	22 (18)
pN_1	72 (57)
pN_2	24 (19)
pN_3	8 (6)
UICC stage	
I	10 (8)
II	10 (8)
III	55 (44)
IV	51 (40)
Grade	
G1/G2	87 (69)
G3/G4	39 (31)
Liver metastases	
Occurrence of metastases	
Synchronous, one-stage resection	44 (35)
Synchronous, two-stage resection	15 (12)
Metachronous	67 (53)
No. of metastases	
Single	68 (54)
Multiple	58 (46)
Resection of metastases	
Hemihepatectomy	14 (11)
Segmentectomy	26 (21)
Atypical resection	86 (68)
R_0 resection	119 (94)
Hepatoduodenal ligament lymph node involvement	35 (28)

Values in parentheses are percentages or *range. UICC, Union Internacional Contra la Cancrum; pT, pathological tumour; pN, pathological node

of three surgeons who were very experienced in this method was performed in all patients to rule out additional occult metastases in the liver and to determine the margin of excision[15]. During extensive hepatic resection excluding hemihepatectomy, Pringle's manoeuvre was used routinely, in some cases intermittently, while small tumours were removed without blood flow reduction. The parenchymal dissection was performed with an ultrasonic dissector; haemostasis on the resection margins was achieved by infrared coagulation, argon beamer, and sealing with fibrin glue and collagen patches. In all cases, lymph node dissection of the hepatoduodenal ligament was performed, so that the nodal status of this regional lymphatic drainage area of the liver could be assessed histologically[14–16]. In the group with R_0 resection of the metastasis ($n = 119$), a mean of 2·8 (range 1–6) lymph nodes were removed; in the group without lymph node involvement 2·7 (range 1–5) ($n = 84$) and in the group with lymph node infiltration 3·1 (range 1–6) ($n = 35$).

In 86 patients an anatomically oriented atypical resection was carried out. The prime aim of this resection was to achieve a free resection margin of at least 1 cm and the resection line was oriented at the intrahepatic vascular structures with the help of intraoperative ultrasonography. In 26 patients, a typical segmentectomy was performed[17]; among these were ten bisegmentectomies and four trisegmentectomies. Fourteen patients underwent hemihepatectomy (six right-sided, eight left-sided), which was carried out as an extended resection in three.

All patients were followed up according to the surgical department's oncological outpatient care programme: at 3-month intervals during the first year and at 6-month intervals thereafter. Each investigation included basic clinical examinations and measurement of carcinoembryonic antigen level as well as colonoscopy, ultrasonography, CT and chest radiography. There was 100 per cent follow-up of the patients until 30 June 1995 with a median follow-up of 46 (range 3–81) months.

Survival curves were calculated according to Kaplan–Meier, and 5-year survival rates were calculated together with the 95 per cent confidence interval, including postoperative deaths and non-tumour-related deaths[18,19]. Univariate and multivariate analysis of the prognostic factors and proportional hazard regression analysis were performed according to Cox[20]. Multivariate χ^2 and P values were used to characterize the independence of these factors; the relative risk [expected (β)] was used to quantify the dependence of survival on each independent variable. The level of significance was defined as $P < 0·05$. Statistical calculations were performed with the use of BMDP Statistical Software, revision 1990 (BMDP, Cork, Ireland) with the use of modules 1L and 2L.

Results

Early postoperative outcome

Postoperative complications occurred in 21 per cent of the patients: intraperitoneal abscess (one patient), intraperitoneal haematoma (eight), bile leakage (six) and secondary wound healing (11). All of the observed abscesses, haematomas and bile leaks showed complete remission after adequate drainage. There were two deaths within 30 and 90 days (2 per cent), one from septic multiorgan failure on day 12 after operation and one fatal bleeding complication on day 23.

In 119 patients (94 per cent), complete (R_0) resection of the liver metastases was achieved. The median excision margin in patients who had R_0 resection was 2·3 (range 0·2–3·1) cm. The incidence of infiltrated lymph nodes in the hepatoduodenal ligament was 28 per cent (35 of the 126 patients with definite histology from this region). Based on the total of 149 patients, including the 23 for whom the hepatoduodenal ligament had been evaluated only macroscopically, this rate was 23 per cent.

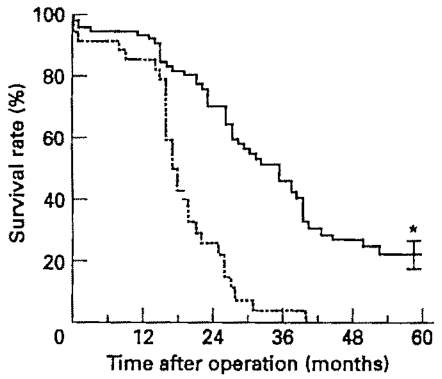
Long-term outcome

The 3- and 5-year survival rates of the 126 patients were 31 and 14 per cent respectively. The group with complete resection of the metastasis (R_0) had 3- and 5-year survival rates of 34 and 15 per cent respectively, while none of the patients with macroscopic or microscopic residual tumour survived more than 3 years. Thus, for the determination of other prognostic factors, only the group of patients who had R_0 resection was analysed. Sex, age (above or below 65 years), pathological tumour (pT) stage of primary tumour and type of resection had no significant relationship with outcome. The multivariate analysis of prognostic factors identified by univariate analysis is listed in *Table 2*. The pathological node (pN) category and grade of the primary tumour were significant variables on univariate but not on multivariate analysis. In multivariate analysis, only the metachronous or synchronous occurrence of the metastases and infiltration of hilar lymph nodes proved to be independent determinants of outcome. The 3- and 5-year survival rates of patients with infiltrated lymph nodes in the hepatoduodenal ligament were 3 and 0 per cent respectively, compared with 48 and 22 per cent in patients without lymph node metastases in this region (*Fig. 1*).

Table 2 Multivariate analysis of significant (univariate) prognostic factors in 119 patients with R_0 resection of colorectal liver metastases

Variable	Relative risk	χ^2	Degrees of freedom	*P*
Colorectal carcinoma pN$_0$ *versus* pN$_{1-3}$		2·50	1	n.s.
Grade (G1,G2/G3,G4)		0·80	1	n.s.
Liver metastases				
No. of metastases (single/multiple)		3 60	1	n.s.
Metachronous/synchronous	1 40 (1 10–1 77)	7 60	1	0·0052
Lymph nodes of hepatoduodenal ligament (infiltrated/not infiltrated)	1·84 (1·41–2 42)	19·20	1	0 0001

Values in parentheses are 95 per cent confidence intervals. pN, pathological node; n.s., not significant



No. at risk						
Nodes not infiltrated	84	67	47	26	13	9
Nodes infiltrated	35	27	7	1	0	0

Fig. 1 Five-year survival curves of 119 patients following R_0 resection of colorectal liver metastases depending on the nodal involvement of the hepatoduodenal ligament – – –, nodes involved; ——, nodes not involved. *95 per cent confidence interval $P < 0{\cdot}0001$ (Kaplan–Meier test)

Discussion

Hepatic metastases of colorectal carcinoma can lead to infiltration of regional lymph nodes in the hepatoduodenal ligament via the lymphatic drainage route of the liver[5,11,14,16,21,22]. This situation has been described as lymphatic remetastasis of liver metastases, as metastases of metastases or as tertiary metastases[3,22,23]. An alternative explanation for this nodal involvement in the hepatoduodenal ligament (i.e. direct lymphogenic metastasis from the primary colorectal carcinoma) is considered unlikely because colorectal carcinomas regularly follow a well defined pattern of lymphogenic metastasis, which does not include the hepatoduodenal ligament. Only if lymph nodes along major mesenteric vessels (N_3 situation) or in the retroperitoneum were involved would further metastatic spread into the hepatoduodenal ligament seem possible[22]. This situation was found in only 6 per cent of the patients presented here, and patients with N_3 metastases of colorectal carcinoma did not show an increased frequency of nodal involvement in the hepatoduodenal ligament. Thus, lymph node metastases in the hepatic hilum are best explained by haematogenous spread from the primary tumour into the liver, growth of these intrahepatic tumour cells and, after connection to the lymphatic drainage of the liver, further metastasis into the regional lymph nodes.

Only a few publications, mostly on small patient groups, deal with the frequency of this lymphogenous spread (*Table 3*). In four of nine series, nodal involvement of the hepatoduodenal ligament was judged on the basis of macroscopic appearance; however, the only certain method of determining nodal infiltration is by histological examination of this lymph node area. The present study evaluated the frequency of regional lymph node involvement of the liver for colorectal metastases in a large group of patients with lymphadenectomy of the hepatoduodenal ligament and subsequent histological examination. The mean number of 2·8 lymph nodes examined demonstrates that the evaluation of the involvement was representative[27]. The rate of 28 per cent found in this study is similar to the rates of 20–30 per cent that were also based on histological examination[10–13] (*Table 3*). Even if the further 23 patients with only macroscopic evaluation of the hilar lymph nodes are included in this calculation, the rate of 23 per cent is still of the same magnitude.

Table 3 Published frequency of regional hepatic lymph node metastasis in the presence of colorectal liver metastases and 5-Year survival rates following resection of liver metastasis in patients with or without infiltration of regional hepatic lymph nodes

Reference	Year	Proportion of patients with hepatic lymph node involvement	Evaluation of nodal status	5-year survival rate (%)*		*P*
				N+	N−	
Fortner *et al.*[21]†	1984	36 of 117 (30 8)	Macroscopic	—	—	0 006§
August *et al.*[22]	1985	7 of 50 (14)	Macroscopic	—	—	—
Hughes *et al.*[24]	1986	24 of 855 (2 8)	Macroscopic	0	33	<0 0001
Ekberg *et al.*[25]	1986	6 of 68 (9)	Macroscopic	0	20	0 01
Ekberg *et al* [10]	1987	6 of 30 (20)	Histological	0	18	0·03
Chang *et al.*[11]†	1987	8 of 24 (33)	Histological	0	20	0·02
Rosen *et al* [12]	1992	9 of 40 (22)	Histological	0	37	0 002
Nakamura *et al* [13]	1992	6 of 22 (27)	Histological	40‡	44	n s
Elias *et al* [26]	1996	14 of 100 (14)	Histological	—	—	—
Present study	1997	35 of 126 (27·8)	Histological	0	22	<0 0001§

Values in parentheses are percentages. *Survival rates in patients with (N+) or without (N−) infiltration of regional hepatic lymph nodes, †irresectable liver metastases treated by intra-arterial chemotherapy, ‡with reresection of hepatic metastases and excluding postoperative deaths n.s, Not significant §Multivariate analysis

It is important to state that nodal involvement of the hepatoduodenal ligament in colorectal liver metastases represents a crucial prognostic factor for the resection of metastases In patients with R_0 resection of metastases, this variable was the most important independent prognostic factor and was associated with the highest relative risk (*Table 2*). The prognostic significance of this factor should be regarded as similar to that of residual tumour state, because the presence of infiltrated hepatic lymph nodes in spite of complete removal of liver metastases is equivalent to leaving residual tumour behind[14]. The prognostic significance of regional lymph node involvement of the liver is confirmed by the reports of others[10,12,24,25] (*Table 3*). In principle, this unfavourable prognostic factor also becomes evident in the two series with intra-arterial chemotherapy of hepatic metastases[11,21].

The overall 5-year survival rate of 14 per cent in the present study seems to be inferior to other published values[2,4–6]; however, in contrast to this analysis, most other studies have not included patients with enlarged hilar lymph nodes and have excluded postoperative deaths as well as non-tumour-related deaths for the calculation of survival.

Because the involvement of hepatic lymph nodes drastically lowers the chance of an improvement in survival time by resection, several authors (with the exception of those using adjuvant therapy protocols) take the position that such a situation no longer represents an indication for the resection of liver metastases[3,12,24,25,28,29]. In the present patients, the survival curve of patients with infiltrated hepatic lymph nodes for the first 15 months is practically parallel to the curve of those without lymphatic involvement (*Fig. 1*). This observation implies that temporary improvement in survival can be achieved by resection of liver metastases in the lymph node-positive group, because the median survival is significantly longer than that in patients with residual intrahepatic tumour: 17·0 (range 15·6–18·4) *versus* 8·0 (6·7–9·3) months ($P < 0{\cdot}05$).

The question remains open as to whether or not systematic radical lymphadenectomy of the hepatoduodenal ligament and along the common hepatic artery could create an 'R_0' situation with improved prognosis[26]. In the literature, there is only one study of this question[13] (*Table 3*). In this small series a favourable effect of lymphadenectomy was indeed shown; the present authors therefore recommend radical lymphadenectomy of the hepatic pedicle during curative resection of colorectal liver metastases[26].

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Expression of oestrogen receptor and oestrogen-inducible genes in pancreatic cancer

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Background Previous studies have not been able to demonstrate convincingly whether the human pancreas expresses oestrogen receptor and whether there is any benefit from antioestrogen therapy in advanced pancreatic cancer.

Methods Oestrogen receptor expression was assessed in normal human pancreas and pancreatic cancer tissue by enzyme immunoassay, Northern blot analysis, *in situ* hybridization and immunohistochemistry. The expression of the oestrogen-inducible proteins, progesterone receptor, pS2 and ERD5 was also examined.

Results A mean of 1·0 (range 0–2·4) fmol oestrogen receptor per mg protein was detected in normal pancreas and 0·5 (range 0–1·2) fmol mg^{-1} in pancreatic cancer. Messenger RNA for oestrogen receptor was detected in both normal and cancerous pancreas. *In situ* hybridization and immunohistochemistry, however, failed to localize oestrogen receptor expression. Mean (range) expression of progesterone receptor in normal and neoplastic pancreas was 1·9 (0·5–3·5) and 2·5 (0·3–9·3) fmol mg^{-1} respectively. pS2 and ERD5 were also expressed in normal tissue and pancreatic cancer, and expression was localized to ductular epithelium.

Conclusion The amount of oestrogen receptor detected in pancreatic tissue was small, and may account for previous difficulties in its detection. The extent to which it is functional in both the normal and malignant pancreas warrants further investigation.

The causes of pancreatic cancer are largely unknown, but the disease tends to be more common in men than women[1], suggesting some role for oestrogen. Although this ratio is supported by some experimental models of pancreatic cancer[2,3], tobacco smoking[4] may account for at least some of the apparent sex difference as the incidence in men has now levelled while that in women is still rising[5,6]. Tamoxifen has been tested as a treatment for advanced pancreatic cancer, but the trial results have been disappointing[7–10].

A requisite for tissue oestrogen responsiveness is the presence of oestrogen receptor. Oestrogen receptor expression was observed in mouse pancreas over three decades ago using an autoradiographic technique[11], but it is still uncertain whether receptor is expressed in human pancreas. Greenway *et al.*[12], using the more specific technique of radioligand binding assay, found binding of oestrogen in pancreatic cancer but not in normal pancreas. Immunohistochemistry for oestrogen receptor in the pancreas has also been reported to be negative[9], as has a specific enzyme immunoassay[13]. Because of the controversies surrounding the role of oestrogen in pancreatic cancer a combination of different techniques including enzyme immunoassay, Northern blot analysis, *in situ* hybridization and immunohistochemistry was used to determine expression of oestrogen receptor as well as that of the oestrogen-inducible genes, pS2, ERD5 and progesterone receptor[14,15].

Patients and methods

Tissue samples were taken from cancerous and normal pancreas for receptor analysis. Samples were snap-frozen into liquid nitrogen immediately after surgical resection and were stored at −70°C. The tissue samples were from patients with primary ductal pancreatic adenocarcinoma (nine men and four women), with a mean age of 55 (range 30–75) years. The presence of cancer in tissue samples was confirmed by histopathology. Tissue from one patient with chronic pancreatitis was also taken.

Northern blot analysis

Total RNA was extracted by the single-step guanidinium isothiocyanate method[16] RNA integrity was assessed by the visualization of distinct ribosomal 28S and 18S bands on a 1 per cent agarose gel stained with ethidium bromide. Northern blot analysis was performed by electrophoresis of approximately 30 μg total RNA in a 1 per cent agarose gel containing 15 per cent formaldehyde in buffer containing morpholinopropanesulphonic acid 20 $mmol\,l^{-1}$. RNA was transferred for 3 h in sodium hydroxide 0·05 $mol\,l^{-1}$ to Hybond N+ nylon membrane (Amersham International, Amersham, UK)

Complementary DNA and membrane hybridization

The partial complementary DNA (cDNA) clone pOR3 of the human oestrogen receptor[17] was obtained from the UK DNA Probe Bank, Medical Research Council, Harrow, UK. A full-length cDNA probe was used for ERD5[18]. The pS2 cDNA was cloned by the polymerase chain reaction (PCR) using the primers 3′GGAATTCGCGAGGCCCAGACAGAGACG5′ and 5′GCTCTAGATCTAAAATTCACACTCCTCTTCTGGAGG3′[14] Probes were validated by multiple restriction enzyme digestions and sequencing To determine total RNA loading, Northern blots were probed with a cDNA cloning for the rat 18S ribosomal RNA[19].

Probes were radiolabelled with [$\alpha^{32}P$]deoxycytidine triphosphate (3×10^3 Ci $mmol^{-1}$) using the random primary extension technique to an activity of 1×10^9 c.p m. μg^{-1}. Membranes were hybridized overnight in a buffer comprising sodium phosphate 0·77 $mol\,l^{-1}$, ethylenediamine tetra-acetic acid (EDTA)

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5 mmol l^{-1}, 7 per cent sodium dodecyl sulphate (SDS) and denatured salmon sperm DNA 100 μg ml^{-1} at 65°C in a rotating oven (Hybaid, Teddington, UK). Membranes were washed in 1 × SSC buffer (sodium citrate 0·015 mol l^{-1}, sodium chloride 0·15 mol l^{-1}) and 1 per cent SDS at 65°C for 1 h, followed by 0·1 × SSC and 0·1 per cent SDS at 65°C for 15 min. The membranes were autoradiographed at −70°C with intensifying screens. Membranes were then stripped at 70°C in 0·5 per cent SDS and reprobed after all activity had been demonstrated by autoradiography to have been removed. Autoradiograms were analysed by laser densitometry (LKB Ultroscan; Pharmacia Biosystems, Milton Keynes, UK).

Total RNA from the human breast carcinoma cell line MCF-7 was also analysed to provide a positive control for oestrogen receptor and oestrogen-inducible genes.

In situ *hybridization for oestrogen receptor and pS2*

In situ hybridization for oestrogen receptor and pS2 was performed to localize expression of messenger RNA (mRNA)[20]. Briefly, antisense riboprobes were transcribed with SP6 RNA polymerase (Promega Biotechnology, Southampton, UK) from the EcoRI–BalI fragment of the oestrogen receptor subcloned into pGEM3 (Promega). The antisense probe for pS2 was made using SP6 RNA polymerase and EcoRI-linearized pSP73 containing the EcoRI–BglII fragment of the PCR clone. Probes were labelled with ^{35}S-radiolabelled uridine 5′-triphosphate to a specific activity of 0·8–1·7 × 10^{9} d.p.m. per μg RNA. Sections (5 μm) of formalin-fixed, paraffin-embedded material were mounted on 3-aminopropyl-triethoxysilane-treated glass slides, dewaxed, and hydrated in phosphate-buffered saline. Sections were permeabilized with proteinase K, postfixed in 4 per cent paraformaldehyde, acetylated then incubated overnight at 55°C in 10–20 μl hybridization mix (sodium chloride 300 mmol l^{-1}, sodium hydrogen phosphate 10 mmol l^{-1}, Tris–hydrochloric acid 10 mmol l^{-1}, EDTA 5 mmol l^{-1}, 0·02 per cent bovine serum albumin, 0·02 per cent Ficoll 400, 0·02 per cent polyvinyl pyrolidone, 50 per cent formamide, bovine ribosomal RNA 0·5 mg ml^{-1}, 10 per cent dextran sulphate, dithiothreitol 10 mmol l^{-1}). Some 1–2 × 10^{6} c.p.m. of probe was added to each slide. Posthybridization washes included a ribonuclease A step and reached a final stringency of 0·5 × SSC at 65°C. Sections were dehydrated in alcohols containing ammonium acetate 300 mmol l^{-1}, dried, dipped in Ilford K5 emulsion (Ilford, Knutsford, UK), and exposed for 3–9 weeks at 4°C before development of silver grains in Kodak D19 (Kodak, Hemel Hempstead, UK). Sections were counterstained using the Giemsa method. Hybridization with oestrogen receptor sense riboprobe transcribed with T7 polymerase provided a control to estimate non-specific hybridization. Hybridization with β-actin antisense riboprobe was performed to demonstrate the presence of hybridizable mRNA in the blocks sectioned.

Enzyme immunoassay for oestrogen and progesterone receptors

Commercially available immunoassays were used according to the manufacturer's instructions (Abbott Laboratories, Maidenhead, UK). Briefly, the tissue was homogenized on ice in a buffer containing 10 per cent glycerol, HEPES 10 mmol l^{-1} pH 7·4, EDTA 1·5 mmol l^{-1}, potassium chloride 0·4 mol l^{-1}, dithiothreitol 0·5 mmol l^{-1} and sodium molybdate 5 mmol l^{-1}. The homogenate was centrifuged at 16 × 10^{3}g at 4°C. Where possible, concentrated cytosol was prepared using high ratios of tissue-weight to homogenizing buffer volume to obtain assay values above a 3-fmol ml^{-1} detection limit as reported previously[21]. The tissue cytosol and receptor standards provided were incubated with beads coated with a rat antireceptor monoclonal antibody. The beads were washed to remove unbound material. Bound receptor was labelled by incubating with a second monoclonal antireceptor antibody conjugated with horseradish peroxidase. After washing, the beads were incubated with enzyme substrate (hydrogen peroxide and *o*-phenylenediamine hydrochloride), and the colour developed was read on a spectrophotometer set at 492 nm. A standard curve was established and specimen values were determined. Total cytosolic protein was estimated using the Bradford method[22] (Bio-Rad Laboratories, Hemel Hempstead, UK).

Immunohistochemistry for oestrogen receptor, progesterone receptor, pS2 and ERD5

Commercially available monoclonal antibodies were used. Antibodies against the human oestrogen receptor and progesterone receptor were obtained from Dako (High Wycombe, UK) and Abbott Laboratories respectively. Antibodies against pS2 and ERD5 were obtained from CIS Bio International (Gif-sur-Yvette, France) and Amersham International respectively.

Tissue was fixed in neutral buffered formalin before being embedded in paraffin wax. Sections were dewaxed, and endogenous peroxidase was blocked with 0·3 per cent hydrogen peroxide in methanol. Sections to be stained for oestrogen receptor were placed in a microwave oven for 10 min in sodium citrate 7 mmol l^{-1}. Sections were incubated with the primary antibody for 30 min. Primary antibodies were used at the following dilutions: between 1:10 and neat for oestrogen receptor and progesterone receptor, 1:10 for pS2, and 1:4 for ERD5. Sections were then incubated with biotinylated rabbit antimouse (antirat for progesterone receptor) antibody for 35 min, for 30 min in streptavidin–peroxidase and for 2 min in peroxidase substrate (diaminobenzidine and 0·3 per cent hydrogen peroxide) and counterstained with haematoxylin. Control sections were processed as above but omitting the primary antibody.

Statistical analysis

Probability assessment was performed using the Wilcoxon paired rank sum test and Mann–Whitney *U* test for non-parametric continuous variables with $P < 0·05$ taken as the significance level.

Results

Oestrogen receptor

Northern blot analysis identified mRNA for oestrogen receptor in all samples of pancreatic cancer and normal pancreas, and the single sample of chronic pancreatitis. Although there was smearing due to partial RNA degradation, a 6·2-kilobase (kb) transcript was seen in pancreatic tissue identical in size to that expressed by MCF-7 breast cancer cells (*Fig. 1*). After correcting laser densitometry readings for uneven loading by expressing oestrogen receptor mRNA as a ratio of 18S ribosomal RNA, no quantitative difference in oestrogen receptor mRNA expression was seen between cancers and normal tissue. *In situ* hybridization for oestrogen receptor was unsuccessful at localizing expression, although expression was identified in slides of uterine tissue used as a positive control (data not shown).

Using enzyme immunoassay for oestrogen receptor, no receptor was detectable in three cancers and one normal tissue sample. Mean(s.d.) oestrogen receptor level in pancreatic cancer was 0·5(0·2) fmol mg^{-1}, and 1·0(0·2) fmol mg^{-1} in normal tissue, but the difference was not statistically significant ($P = 0·14$). No significant difference was seen in receptor levels in men and women. The receptor concentration in the single chronic pancreatitis specimen was 4·3 fmol mg^{-1}. Immunohistochemistry for oestrogen receptor was not successful at localizing expression, although positive staining was seen on slides of uterine tissue (data not shown).

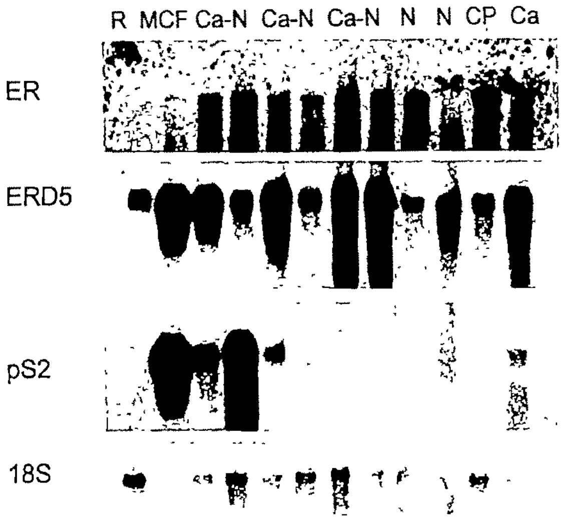

Fig. 1 Expression of messenger RNA for oestrogen receptor and oestrogen-inducible genes, pS2 and ERD5, in pancreatic tissue. Shown are autoradiograms of Northern blots hybridized to complementary DNA probes for oestrogen receptor (ER), ERD5, pS2 and 18S ribosomal RNA. 18S ribosomal RNA indicates the amount of total RNA loaded. R, calf liver ribosomal RNA (negative control); MCF-7, a breast cancer cell line (positive control), Ca, cancer, N, normal pancreas; CP, chronic pancreatitis; Ca-N, paired sample from same patient

Progesterone receptor

Progesterone receptor levels determined by enzyme immunoassay were similar in neoplastic and normal pancreatic tissue (mean(s.d.) 2·5(0·9) and 1·9(0·4) fmol mg^{-1} respectively). All tissues were positive for receptor, even those negative for oestrogen receptor. The chronic pancreatitis specimen had a progesterone receptor concentration of 2·4 fmol mg^{-1}. Immunohistochemistry for progesterone receptor was not successful, despite positive staining of uterine tissue.

pS2

Northern blot analysis demonstrated pS2 mRNA (0·6 kb) in three of four cancers probed, but in only one of six normal tissue samples. Both *in situ* hybridization and immunohistochemistry demonstrated pS2 in malignant epithelium, and in ductules in normal tissue (*Fig. 2a* and *b*).

ERD5

Northern blot analysis identified a single transcript of approximately 1 kb, identical in size to that seen in MCF-7 cells. Immunohistochemistry demonstrated staining in ductules in normal tissue (data not shown) and neoplastic epithelium (*Fig. 2c*).

Discussion

This study has demonstrated mRNA for oestrogen receptor in normal and neoplastic pancreatic tissue and confirmed its presence by enzyme immunoassay. All tissues were also positive for progesterone receptor by immunoassay.

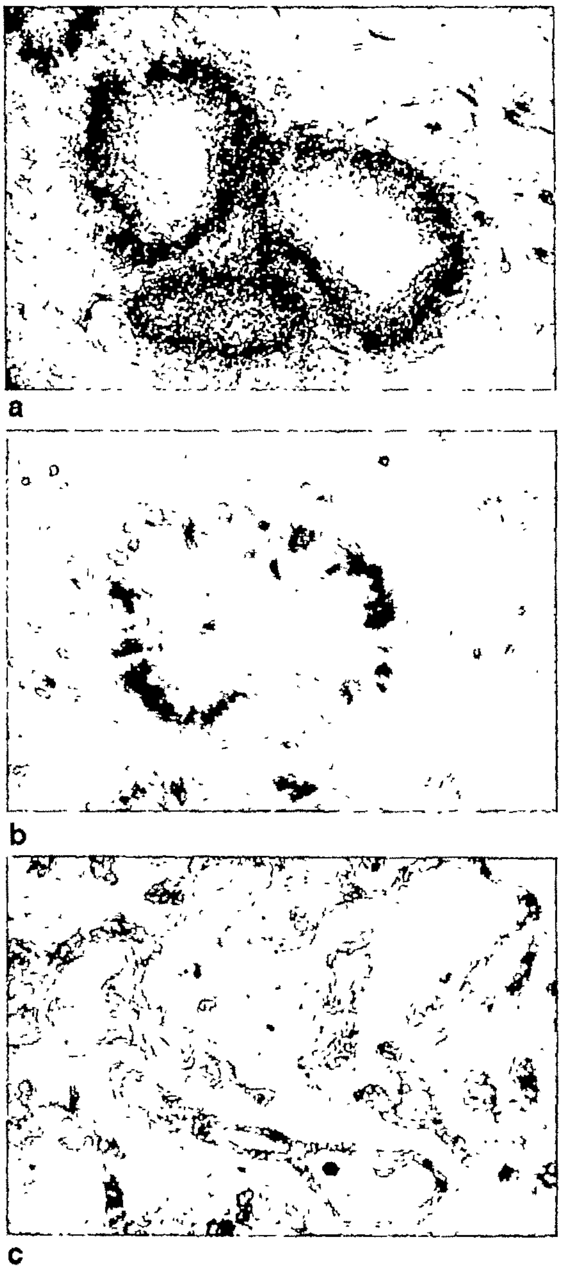

Fig. 2 a *In situ* hybridization and b immunohistochemistry for pS2 in normal pancreatic ducts; pS2 messenger RNA and protein are expressed in pancreatic ducts. c Positive immunostaining for ERD5 in a pancreatic adenocarcinoma (original magnification × 250)

The inability to demonstrate receptors by *in situ* hybridization and immunohistochemistry is almost certainly a consequence of the small amount of receptor expressed and the particular difficulties in handling pancreatic tissue due to the presence of large amounts of ribonucleases.

Previous studies have documented binding of oestrogen to pancreatic tissue. Ullberg and Bengtsson[11] reported concentration of systemically administered oestrogen in mouse pancreas and Greenway *et al.*[12] observed binding of oestrogen in pancreatic cancer but not in normal pancreas; the binding capacity was too high to be due to the oestrogen receptor itself. Taylor *et al.*[9] were unable to detect oestrogen receptor by immunohistochemistry as in the present study. The low amount of oestrogen receptor protein detected by enzyme immunoassay was below the threshold of detection of conventional radioligand binding assays, taking 10 fmol per mg protein as the zero threshold. Targarona *et al.*[13] did not detect oestrogen receptor by enzyme immunoassay, but the high cytosolic protein concentrations that were found to be essential to obtain measurable values of receptor in this study were probably not used.

Expression of the oestrogen-inducible genes pS2[14] and ERD5[15] was detected in normal and neoplastic pancreas. ERD5 and oestrogen receptor are closely associated, and antibody to ERD5 can immunoprecipitate ligand-bound oestrogen receptor[23]. ERD5 expression may be correlated with specific binding of oestrogen in breast tissue[24], although not invariably so[25], and ERD5 expression may have similar prognostic significance to that of oestrogen receptor expression in breast cancer[26]. Expression of pS2 in normal pancreatic ductules and ERD5 immunostaining in pancreatic cancers with abnormal transcript lengths has been shown previously[27]. Several autocrine loops have been strongly implicated in the pathogenesis of pancreatic cancer[28], which possibly explains the expression of pS2, ERD5 and progesterone receptor. Epidermal growth factor can induce pS2[29], while insulin-like growth factor 1 induces expression of progesterone receptor[30], which may be an alternative explanation for the finding of progesterone receptor in the absence of oestrogen receptor in some samples.

The amount of oestrogen-receptor detected in pancreatic tissue was extremely small, very much less than that in normal breast tissue[31], and even less than that in large bowel[21,32] or stomach[33]. The presence in pancreas of the enzymes oestrone sulphatase[34] and aromatase[35], which are involved in local synthesis of oestrogens, provides indirect evidence that the oestrogen receptor in pancreas is functional. Oestrogen treatment has been reported to reduce pancreatic weight in guinea-pigs[36], and has been claimed by some, but not others, to inhibit the growth of pancreatic xenografts[37,38].

Tamoxifen, an oestrogen antagonist, but also a partial agonist, has been proposed as a therapy for patients with pancreatic cancer. A case–control study[10] of 80 patients with pancreatic cancer treated with tamoxifen reported a median survival of 7 months, compared with 3 months in controls. The median survival in women aged over 60 years treated with tamoxifen, however, was 12 months. One of three randomized studies reported a median survival time of 5·3 months in 37 tamoxifen-treated patients and 3 months in 39 controls ($P = 0{\cdot}09$)[7]. The study by Bakkevold *et al.*[8] reported no survival advantage in 92 patients randomized to tamoxifen treatment (median survival 115 days) compared with 84 patients in the placebo group (median survival 122 days). Subgroup analysis demonstrated significantly longer survival in women with stage III disease, but not when all women randomized to the trial were included. In the most recent study the median survival was 75 days in 22 patients randomized to tamoxifen treatment compared with 131 days in the 22 controls[9]. In none of the three randomized trials[7–9] were there sufficient numbers to support or refute the findings of Wong and Chan[10] that the survival benefit of tamoxifen treatment is most evident in postmenopausal women.

The equivocal findings of trials with antioestrogen therapy in pancreatic cancer are not surprising given the low and variable amount of oestrogen receptor present. It may be that, as for breast cancer, the benefits of antioestrogen therapy in pancreatic cancer are seen mainly in those who express the greatest amount of receptor. Future trials of antioestrogen therapy might examine the response based on amount of receptor expressed and should also use a drug with purer antioestrogenic activity than tamoxifen, which is a partial agonist.

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Lymph node metastasis in carcinoma of the body and tail of the pancreas

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Background There have been no precise reports concerning lymph node metastatic involvement in carcinoma of the body and tail of the pancreas.

Methods Histopathological examination of lymph node involvement in 30 specimens obtained from patients who underwent pancreatic resection and wide dissection of lymph nodes, including para-aortic lymph nodes, for carcinoma of the body and tail of the pancreas was performed.

Results Fourteen of 30 patients had lymph node involvement. The highest incidence of lymph node involvement was around the splenic artery (five of 30 patients), aorta (four of 30) and coeliac trunk (four of 30). No significant difference in survival rate between the lymph node-negative group and the lymph node-positive group was observed, but all patients in the positive group died within 2 years after surgery, and four patients with para-aortic lymph node involvement died from recurrence within 10 months after surgery. Survival rates were significantly worse in patients with histopathological extrapancreatic nerve plexus invasion, retropancreatic tissue invasion, tumour diameter more than 4 cm, histological portal system vein wall invasion and carcinoma invasion of the surgical margins.

Conclusion Although aggressive extended surgery including para-aortic node dissection has been performed, the postoperative survival rate is still low in patients with carcinoma of the body and tail of the pancreas. The high incidence of liver metastasis after surgery is a prime cause of the poor outcome, and effective therapy for postoperative liver recurrence requires evaluation.

Lymph node dissection is an important component of radical surgery for carcinoma of the pancreas. Patients with a tumour of the body and tail are often diagnosed at a late stage because of the vague non-specific symptoms[1]. The resectability rate of carcinoma of the body and tail of the pancreas is low compared with that of carcinoma of the head of the pancreas[2]. There have been no precise reports concerning lymph node metastatic involvement in carcinoma of the body and tail of the pancreas.

Histopathological studies of lymph node involvement have practical use and are helpful for guiding operative therapy. The present study was undertaken using resected specimens to evaluate the extent of lymph node involvement in carcinoma of the body and tail of the pancreas.

Patients and methods

Between 1981 and 1995, 62 patients with ductal carcinoma of the body and tail of the pancreas were admitted to this department. Fifty-seven of 62 patients were operated on and 36 underwent resection. Lymph node dissection including para-aortic lymph nodes was performed in 30 of 36 patients who had resection. Specimens from these 30 patients were subjected to histopathological studies Operative procedures are shown in *Table 1*. The age of the 30 patients ranged between 43 and 75 (mean 61·6) years and there were 24 men Portal vein resection was performed using catheter bypass of the portal vein[3]. Because of carcinoma invasion in four patients, the coeliac and common hepatic artery (two patients) and common hepatic artery alone (two patients) were resected and reconstructed Intraoperative irradiation therapy was administered to 19 of 30 patients.

Table 1 Operative procedures for carcinoma of the body and tail of the pancreas

	No. of patients ($n = 30$)
Total pancreatectomy	6 (6)
Subtotal distal pancreatectomy	9 (5)
Distal pancreatectomy	15 (0)

Values in parentheses indicate the number of portal vein resections

Histopathological findings were evaluated in accordance with the General Rules for Surgical and Pathological Studies on Cancer of the Pancreas proposed by the Japan Pancreas Society[4]. The nomenclature of the major lymph nodes is defined in *Fig 1*[5]. The area of para-aortic lymph node dissection extended from the coeliac trunk to the inferior mesenteric trunk and from the right margin of the inferior vena cava to the left margin of the abdominal aorta (*Fig 2*). Survival, including postoperative death, was calculated by the Kaplan–Meier method. Statistical analysis was performed with the generalized Wilcoxon test. The significance of the correlation between two factors was evaluated by the χ^2 test P values less than 0·05 were considered statistically significant.

Results

The number of lymph nodes dissected in each patient ranged between seven and 77 (mean 30·8).

The frequency of lymph node involvement is given in *Table 2*. Fourteen of the 30 patients with carcinoma of the body and tail of the pancreas had lymph node involvement. A relatively high incidence of lymph node involve-

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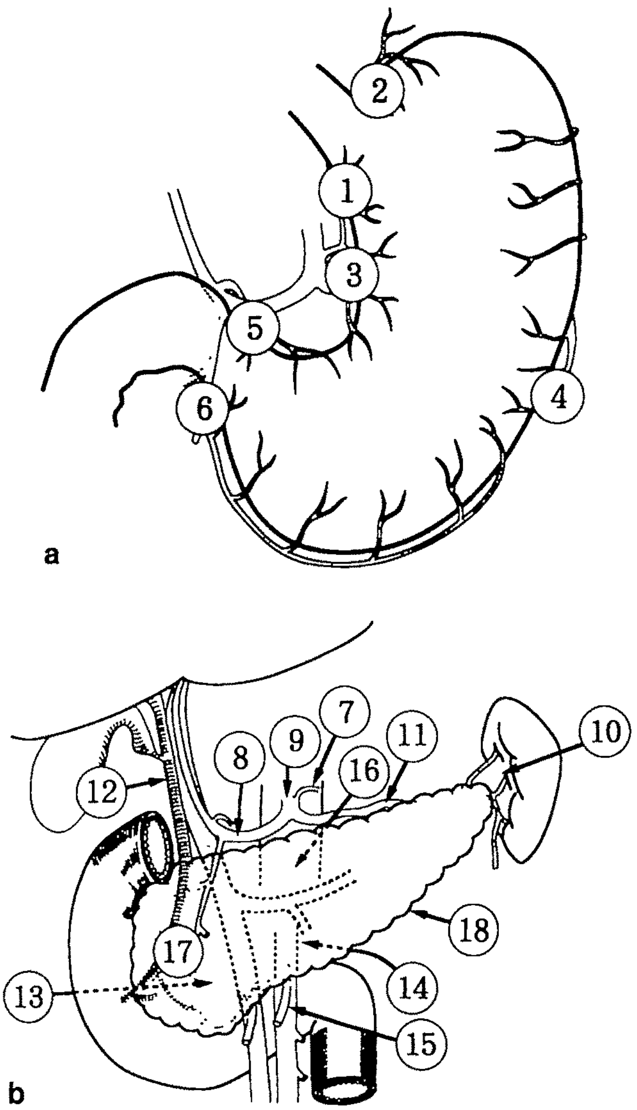

Fig. 1 Nomenclature of a perigastric lymph nodes in patients with carcinoma of the body and tail of the pancreas, and b lymph nodes in the region of the body and tail of the pancreas: 1, right cardiac nodes; 2, left cardiac nodes; 3, lesser curvature nodes; 4, greater curvature nodes, 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes around the left gastric artery; 8, nodes around the common hepatic artery; 9, nodes around the coeliac trunk, 10, nodes at the hilus of the spleen, 11, nodes along the splenic artery; 12, nodes of the hepatoduodenal ligament; 13, posterior pancreaticoduodenal nodes; 14, nodes around the superior mesenteric artery; 15, nodes along the middle colic artery; 16, para-aortic nodes; 17, anterior pancreaticoduodenal nodes; 18, inferior pancreatic body nodes

ment was observed along the splenic artery, around the superior mesenteric artery, around the aorta and around the coeliac trunk. A low incidence of lymph node involvement was observed on the inferior pancreatic body, around the common hepatic artery, at the hilus of the spleen, on the anterior surface of the head of the pancreas, on the lesser curvature and in the infrapyloric region.

Table 3 shows involvement of other lymph node groups in four patients who had para-aortic lymph node involvement. Lymphatic flow from the tumour to the para-aortic lymph nodes via lymphatics around the superior mesenteric artery was suspected in Patients 1 and 2. Lymphatic flow from the tumour to the para-aortic lymph nodes around the coeliac trunk was suspected in Patient 3. Direct lymphatic flow from the tumour to the para-aortic lymph nodes was suspected in Patient 4.

There was no correlation between lymph node involvement and various other factors such as tumour size, capsular invasion, extrapancreatic nerve plexus invasion or portal system vein wall invasion.

Postoperative deaths (within 30 days after operation) occurred in two of the 30 patients. The 1-, 2-, 3- and 5-year cumulative survival rates, including postoperative deaths, in the lymph node-negative group were 29, 20, 10 and 10 per cent respectively. One- and 2-year survival rates of the lymph node-positive group were 21 and 10 per cent respectively, reflecting no statistically significant difference. All 15 patients with a tumour more than 4 cm in size died within 1 year, whereas 1-, 3- and 5-year survival rates for 15 patients with tumour less than 4 cm

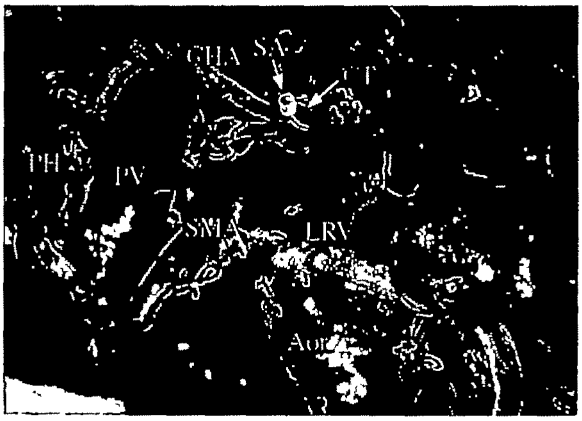

Fig. 2 Retroperitoneal area after subtotal distal pancreatectomy combined with wide lymph node dissection for carcinoma of the body and tail of the pancreas. Aor, aorta; CHA, common hepatic artery; CT, coeliac trunk; LRV, left renal vein; PH, pancreatic head; PV, portal vein; SA, splenic artery; SMA, superior mesenteric artery

Table 2 Lymph node involvement in patients with carcinoma of the body and tail of the pancreas

Lymph node group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Involvement ($n = 30$)	0	0	1	0	0	1	0	1	4	1	5	0	0	4	0	4	1	2

Lymph node groups are defined in *Fig. 1*

Table 3 Lymph node metastases in four patients with involvement of para-aortic lymph nodes

	Lymph node group												
	3	4	5	6	7	8	9	10–13	14	15	16	17	18
Patient 1	–	–	–	–	–	–	–	–	+	–	+	–	–
Patient 2	+	–	–	+	–	–	–	–	+	–	+	+	–
Patient 3	–	–	–	–	–	–	+	–	–	–	+	–	–
Patient 4	–	–	–	–	–	–	–	–	–	–	+	–	–

were 43, 14 and 14 per cent respectively ($P<0\cdot05$). All 21 patients with retropancreatic tissue invasion died within 1 year, whereas 1-, 3- and 5-year survival rates for nine patients with no retropancreatic tissue invasion were 67, 44 and 22 per cent respectively ($P<0\cdot01$). All 14 patients with extrapancreatic nerve plexus invasion died within 1 year, whereas 1-, 3- and 5-year survival rates for 16 patients without extrapancreatic nerve plexus invasion were 36, 12 and 12 per cent respectively ($P<0\cdot05$). All 11 patients with portal system vein wall invasion died within 1 year, whereas 1-, 3- and 5-year survival rates for 19 patients without portal system vein wall invasion were 30, 10 and 10 per cent respectively ($P<0\cdot01$). All 13 patients with invasion of surgical margins died within 1 year, whereas 1-, 3- and 5-year survival rates for 17 patients with negative surgical margins were 36, 12 and 12 per cent respectively ($P<0\cdot05$).

Discussion

Lymph node dissection is an important component of radical surgery for pancreatic carcinoma. There have been many histopathological studies concerning lymph node involvement in pancreatic head carcinoma[5–8]. However, there have been no precise studies concerning lymph node involvement in carcinoma of the body and tail of the pancreas. This may be because the resectability rate is low, leading to few resectable cases of carcinoma of the body and tail of the pancreas in each hospital, and the fact that para-aortic lymph node dissection has not yet been performed routinely.

In 1981, the authors developed an antithrombogenic bypass catheter of the portal vein[3], and isolated pancreatectomy[9] combined with portal vein, hepatic artery and superior mesenteric artery resection has been performed, using the catheter bypass procedure to prevent portal congestion and hepatic ischaemia[10]. Para-aortic lymph node dissection has also been performed aggressively.

The incidence of lymph node involvement in carcinoma of the body and tail is lower than that in carcinoma of the head of the pancreas, which was 77 per cent in the authors' series[5]. In carcinoma of the head of the pancreas, lymphatic flow was strongly suspected from the tumour to the para-aortic lymph nodes via the posterior surface of the pancreatic head and around the superior mesenteric artery[5,8]. However, the present findings in carcinoma of the body and tail of the pancreas suggest three lymphatic flow pathways from the tumour to the para-aortic lymph nodes. The first is a pathway around the superior mesenteric artery, the second a route around the coeliac artery and the third a direct pathway from the tumour to the para-aortic lymph nodes. However, more data are needed to clarify the lymphatic flow.

No statistically significant difference in survival rates was observed between patients with and without lymph node involvement, but all patients in the lymph node-positive group died within 2 years after surgery and four patients with para-aortic lymph node involvement died within 10 months of operation from recurrence. Significantly worse survival rates were observed in patients with histopathological extrapancreatic nerve plexus invasion, retropancreatic tissue invasion, tumour size more than 4 cm, histological portal system vein wall invasion and carcinoma invasion of the surgical margins.

Although aggressive extended surgery, including portal vein resection and para-aortic lymph node dissection has been performed, the postoperative survival rate is still low in patients with carcinoma of the body and tail of the pancreas. Lymph nodes most often involved by tumour in these patients are those along the splenic artery, superior mesenteric artery and around the coeliac trunk. The high incidence of liver metastasis after surgery is a prime cause of the poor outcome, and effective therapy for post-operative liver recurrence requires evaluation.

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Short note

Magnetic resonance imaging of bone metastases: a diagnostic and screening technique

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Preoperative isotope bone scans have a low sensitivity for metastases. Magnetic resonance imaging (MRI) is useful for the detection of bone disease in haematological malignancy[1] and to differentiate between causes of vertebral compression fracture in advanced breast cancer[2].

The sensitivity of MRI and scintigraphy was compared in the investigation of bone pain developing in patients during follow-up after cancer surgery. MRI was also assessed as a preoperative staging procedure.

Methods

Bone scintigraphy was performed by standard methods using ^{99m}Tc-labelled disphosphonate. MRI was performed on a Siemens Magnetom Impact Expert 1 0 tesla scanner (Erlangen, Germany). Spin echo (SE) T_1W and Short Time Inversion Recovery (STIR) sagittal sequences of the thoracolumbar spine and SE T_1W and STIR coronal sequences of the pelvis and upper femora were obtained for each patient. MRI was considered positive for metastasis when there was a focal decrease in signal intensity on SE T_1W images and an increased signal on STIR images, within the bone marrow. χ^2 analysis was used to compare variables.

Results

Investigation of symptomatic patients

Thirty-eight patients with cancer (median age 54 (range 21–59) years) had MRI of bone and isotope bone scans (within 6 weeks of each other) to investigate localized bone pain. An unequivocal diagnosis of metastasis as a cause of pain was made in 24 patients with MRI. The remaining 14 studies were unequivocally negative. Twenty-one isotope scans were unequivocally positive ($n = 13$) or negative ($n = 8$), while seven gave false-negative results (four bone metastases, two soft tissue and bone, one soft tissue alone). MRI led to a change of management in 15 patients (when isotope scans were equivocal ($n = 10$), or by detection of marrow involvement ($n = 4$) or soft tissue disease ($n = 1$)).

Preoperative magnetic resonance imaging

This was performed in 26 women with early breast cancer: six showed metastases (multiple in three patients and single in three). One patient had incipient spinal cord compression and required immediate radiotherapy. Only two of the six patients had abnormal isotope bone scans. A positive scan could not be predicted (*Table 1*) by size or grade of the tumour. However, all six women were subsequently shown to have histologically involved nodes ($P < 0{\cdot}01$).

Table 1 Clinical and histological features of patients with early breast cancer who underwent preoperative magnetic resonance imaging

	MRI positive ($n = 6$)	MRI negative ($n = 20$)
Tumour size (mm)		
Median (range)	20 (10–35)	17 (6–35)
< 20 mm	4	13
Grade III†	1	5
Palpable nodes	1	4
Histological node involvement	6	7*

MRI, magnetic resonance imaging. $^*\chi^2 = 7{\cdot}8$, 1 d.f., $P < 0{\cdot}01$. †Bloom and Richardson classification

Three MRI-positive patients have subsequently relapsed, whereas no recurrence has occurred in the MRI-negative patients ($\chi^2 = 4{\cdot}13$, 1 d.f., $P < 0{\cdot}05$).

Discussion

Isotope bone scanning remains the commonest method used to detect bone metastases[3]. However, false-positive results are frequent and in this study bone scanning gave a sensitivity of 68 per cent and a specificity of 50 per cent, whereas MRI was highly sensitive and specific.

Computed tomography (CT) with myelography is a cheaper alternative to MRI, but CT can produce only axial images, making screening of the whole spinal cord impractical; MRI has been shown to be superior[4].

Preoperative assessment of patients with breast cancer by MRI revealed that six of 26 had demonstrable bone metastases even though the patients were not a particularly bad prognostic group. Neither clinical nor histological features of the tumours predicted overt metastases on MRI. Isotope bone scans were performed only when MRI was positive, but metastases were demonstrated in only one-third of patients. The management of one patient was altered by MRI, because she required radiotherapy for incipient cord compression. Knowledge about the presence of metastases would ensure that patients receive appropriate systemic therapy.

MRI is the most sensitive and accurate technique for detection of skeletal metastases and staging of patients with breast cancer.

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Case report

Retroperitoneoscopic lumbar sympathectomy

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Excision of the lumbar ganglia was first described by Hunter and Royle in Sydney in 1923 and is indicated in patients with unreconstructable vascular disease in the leg, vasospastic disorders, causalgia, cold injury and hyperhidrosis[1,2]. Traditional extraperitoneal lumbar sympathectomy through an iliac fossa incision has recently been replaced by percutaneous chemical ablation using radiographic localization, but this technique is associated with complications and possibly with a higher incidence of incomplete sympathectomy[2,3]. A retroperitoneoscopic technique for lumbar sympathectomy is described.

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Case report

A 49-year-old man presented with symptoms of reflex sympathetic dystrophy in the left foot and sensitivity to phenol. A variety of interventions, including local surgery, failed to relieve the symptoms. Percutaneous bupivacaine and guanethidine blocks produced temporary improvement.

At operation with the patient in a semilateral position, a 1-cm incision was made in the flank to permit finger dissection in the extraperitoneal plane. A 12-mm balloon dissecting port (Origin Medisystem, San Francisco, California, USA) was used to develop the space and the retroperitoneum was then insufflated with carbon dioxide. Iliac fossa and subcostal working ports were inserted under direct vision after identifying the ureter and gonadal vessels The lumbar sympathetic chain was identified on the lateral surface of the lumbar vertebrae (*Fig. 1*) and the sympathetic ganglia were excised from the upper limit of the dissection (renal pelvis) to the pelvic brim. Symptoms were relieved immediately after surgery and remain so at 3 months of follow-up. The procedure took less than 1 h to perform, the

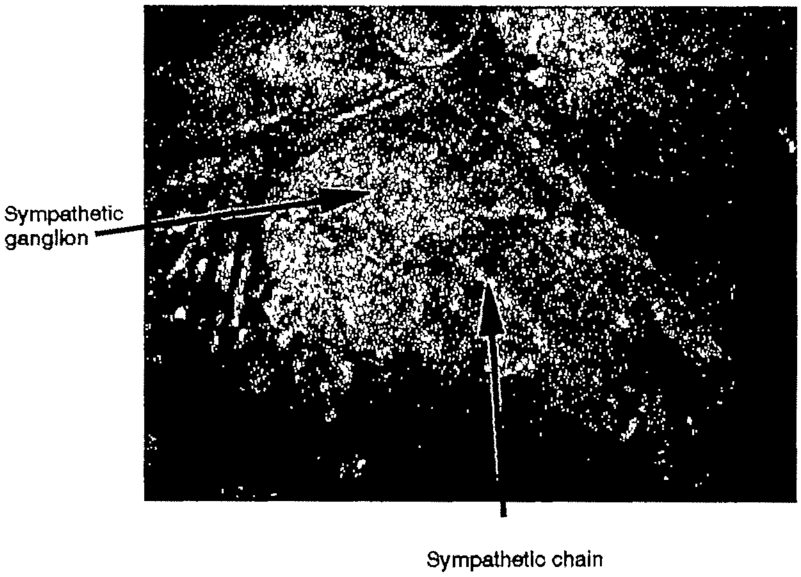

Fig. 1 Retroperitoneoscopic view during lumbar sympathectomy showing the sympathetic chain and ganglia lying on the lumbar vertebrae

patient was able to mobilize and eat immediately, and was discharged 24 h later.

Discussion

Open lumbar sympathectomy allows safe and complete ganglionectomy at the expense of general anaesthesia and a painful muscle-cutting incision. Hospitalization for up to 5 days is usual. Percutaneous chemical sympathectomy can be performed as a day case but the procedure is associated with complications including paralysis, renal and vascular trauma, as well as phenol injury to the ureter and retroperitoneal nerves[1,3]. Studies of the completeness of chemical sympathectomy are inconclusive[4,5].

Retroperitoneoscopic sympathectomy avoids the disadvantages associated with both of these procedures; direct views minimize the risk of injury to retroperitoneal structures and allow complete excision of the sympathetic chain (with histological confirmation). Oral analgesics are adequate, particularly if the port sites are infiltrated with local anaesthetic, and the procedure may be suitable for day case management. However, general anaesthesia is required and the operation may be expensive. The authors believe this operation warrants further consideration in a comparative study with chemical sympathectomy.

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Local anaesthetic for lower-limb revascularization in high-risk patients

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Background A few patients with critical limb ischaemia are believed to be too unfit for an attempt at revascularization using conventional anaesthesia.

Methods A retrospective analysis was undertaken of 46 revascularization procedures performed in high-risk patients for critical limb ischaemia between 1989 and 1995, in which local anaesthetic techniques were utilized in preference to general or spinal anaesthesia.

Results Cumulative survival rates at 6, 12 and 24 months were 67, 57 and 51 per cent. Primary patency rates were 77 per cent at 6 months, 67 per cent at 12 months and 53 per cent at 24 months, with associated limb salvage rates of 87, 87 and 79 per cent.

Conclusion Selective use of local anaesthetic techniques extends the benefits of limb salvage to patients considered unfit for conventional anaesthesia.

The number of surgical procedures for critical leg ischaemia has increased in the past few years, particularly in the elderly[1,2]. Several studies have shown that limb salvage is important in maintaining independence and quality of life in this group[3–5]. Most vascular surgical patients have advanced atherosclerotic disease and a variety of other medical problems complicating the decision to undertake revascularization[6]. Notwithstanding that these procedures are associated with a significant degree of postoperative morbidity and that the long-term prognosis of these patients is poor, it is generally acknowledged that limb salvage is preferable to primary amputation[7–10] The decision to perform primary amputation is, in some cases, based on unsuitability for the prolonged anaesthesia required for arterial reconstructive surgery[4].

Data obtained on the outcome of a group of high-risk patients who had revascularization procedures using local anaesthetic techniques have been analysed.

Patients and methods

This was a retrospective study of patients who had a revascularization procedure under local anaesthesia at Selly Oak Hospital, Birmingham, between January 1989 and December 1995 Clinical data were obtained from patient records. All procedures were performed by one surgeon (M.H S.) and were carried out for critical leg ischaemia as defined in the European Consensus Document[11].

Patients were offered primary amputation only if it was clear that they could not benefit from reconstruction on the following grounds· leg not useful for walking, transferring or balance; extensive ischaemic necrosis of calf muscle; irreversible loss of weight-bearing function; obliteration of all normal run-off arteries in calf or foot as assessed by good quality angiography or surgical exploration.

Patients were excluded from the study if they had simple embolectomy, graft embolectomy or a revision procedure

The patients studied were thought to be unfit for general or epidural anaesthesia after assessment by a consultant anaesthetist The procedures were therefore carried out using local infiltration in the groin and popliteal fossa with closed femoral nerve block and open popliteal sciatic nerve block[12–17] Anaesthesia was achieved with 10–15 ml 0·5 per cent prilocaine for each nerve block. Total volumes of 80–100 ml were used for infrainguinal procedures using either prosthetic or *in situ* saphenous vein. An additional 40 ml was used for harvesting the arm vein. No patient had in excess of the recommended maximum dose of 120 ml, or 600 mg 0·5 per cent prilocaine. Sedation was not used routinely but, if necessary, was achieved with a small dose of opiate or benzodiazepine.

Cumulative survival, graft patency and limb salvage rates were calculated by means of life-table analysis.

Results

A total of 654 patients underwent arterial reconstruction between 1989 and 1995. Some 49 of these procedures were carried out under local and regional anaesthesia on 47 patients; two patients had separate procedures on different limbs during the study. Sixty-seven patients were thought unsuitable for vascular reconstruction on the criteria listed above and were offered primary amputation.

Of the 49 procedures performed under local anaesthesia, three sets of case notes were not traced, leaving 46 procedures available for analysis.

There were 28 men and 18 women with a mean age of 76 (range 49–93) years. Suitability for general anaesthesia was assessed using American Society of Anesthesiologists (ASA) categories[18]. Some 43 patients were categorized as ASA grade 4 and two as ASA grade 5. One patient who had an emergency local anaesthetic procedure was ASA grade 3; this procedure followed an aortobifemoral reconstruction under general anaesthesia earlier in the day which was complicated by perioperative myocardial ischaemia.

Indications for local anaesthesia are outlined in *Table 1*, and procedures done in *Table 2*. Saphenous vein was used in 38 patients, arm vein in seven and a prosthetic graft in four; some patients had a combination. Mean operating time was 155 (range 60–420) min. Two procedures were converted to general anaesthesia. One was in a 91-year-old man who became restless and complained of a painful back after 4 h of surgery. The nerve blocks were noted to be functioning at that time. The second was in a 56-year-old man who became restless while undergoing an axillobifemoral procedure and who had incomplete blocks. No patient experienced any symptoms or signs of local anaesthetic toxicity.

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Table 1 Medical conditions influencing choice of anaesthetic in 46 patients

Condition	No. of patients
Impaired cardiac function	39
Chronic obstructive airway disease	11
Problems with previous general anaesthetic	2
Renal failure	4
Cerebrovascular disease	2
Electrolyte abnormality	2

Table 2 Arterial reconstructions under local anaesthetic included in the study

Procedure	No. of procedures
Axillofemoral graft	2
Femoral crossover graft	2
Sequential jump graft	4
Femorodistal bypass	27
Femoropopliteal bypass	6
Popliteal–pedal bypass	5

Table 3 Cumulative survival rates

Time after operation (months)	No. at risk	No. completing follow-up	No. dead	Interval survival	Cumulative survival
0–1	46	0	10	0·783	1
1–3	36	0	5	0·861	0·783
3–6	31	2	3	0·903	0·674
6–9	26	2	1	0·962	0·609
9–12	23	1	2	0·913	0·568
12–15	20	6	1	0·950	0·535
15–18	13	0	0	1	0·508
18–21	13	0	0	1	0·508
21–24	13	0	0	1	0·508

Perioperative mortality (within 30 days) occurred in ten of the 46 patients. Five patients died from myocardial infarction complicated by cardiac arrest, one from a massive pulmonary thromboembolism, one from a disabling stroke, two from multisystem organ failure and one from mesenteric infarction. A further four patients died before discharge at day 31 (cardiac arrest), day 46 (graft haemorrhage), day 66 (graft haemorrhage with myocardial infarction) and day 78 (multiple organ failure). One of the two patients converted to general anaesthesia during operation died within 2 months in a nursing home; the other was still alive at 6-month follow-up. For the 32 patients who survived to discharge, the mean length of hospital stay was 27 (range 10–82) days. Five patients were transferred to nursing homes or long-stay geriatric units; the remainder returned home.

Cumulative survival rates are shown in *Table 3* and primary patency and limb salvage rates are depicted in *Tables 4* and *5*.

Seven revision procedures were carried out within 1 month. Three patients required below-knee amputation and three had an above-knee amputation following unsuccessful embolectomy. One patient had revision of a femorodistal graft using arm vein. With the exception of one patient who had a below-knee amputation under short general anaesthesia, all amputations and graft revisions were carried out under local anaesthesia.

Table 4 Cumulative graft patency

Time after operation (months)	No. at risk	No. dead	No. completing follow-up	No. failed	Interval patency	Cumulative patency
0–1	46	9	0	8	0·826	1
1–3	29	2	0	2	0·931	0·826
3–6	25	2	2	2	0·920	0·769
6–9	19	0	2	1	0·947	0·707
9–12	16	1	1	1	0·938	0·670
12–15	13	1	6	2	0·846	0·628
15–18	4	0	0	0	1	0·532
18–21	4	0	0	0	1	0·532
21–24	4	0	0	0	1	0·532

Table 5 Cumulative limb salvage

Time after operation (months)	No. at risk	No. dead	No completing follow-up	No. amputated	Interval limb salvage	Cumulative limb salvage
0–1	46	9	0	6	0·870	1
1–3	32	2	0	0	1	0·870
3–6	30	2	2	0	1	0·870
6–9	26	0	2	0	1	0·870
9–12	24	1	1	0	1	0·870
12–15	22	1	6	2	0·909	0·870
15–18	13	0	0	0	1	0·791
18–21	13	0	0	0	1	0·791
21–24	13	0	0	0	1	0·791

Discussion

Patients with limb-threatening ischaemia are offered either primary amputation or reconstructive surgery. Successful limb salvage returns patients to an independent lifestyle and improves their quality of life. There is a small group of people who are perceived as being at too great a risk to undergo revascularization because of concurrent medical problems. The authors were able to offer arterial reconstruction to some in this group, using local anaesthetic techniques.

There have been several studies advocating the use of epidural anaesthesia for lower-limb revascularization[19,20]. Epidural anaesthesia is, however, associated with a significant risk of hypotension due to sympathetic blockade. Regional techniques provide blockade of the stress response to surgery, avoidance of the hyperdynamic response to tracheal intubation and a reduced risk of postoperative respiratory infection[21,22]. There is some evidence that regional anaesthesia may prevent postoperative hypercoagulability[23] and reduce the incidence of vascular graft complications[24]. Anaesthesia has previously been described by sciatic nerve block for certain vascular procedures below the knee including amputation and debridement[25]. In the present study revascularization was attempted under peripheral regional block.

Life expectancy in this particular high-risk group of patients is poor, with a cumulative survival rate of 50 per cent at 24 months. The majority of perioperative and postoperative deaths were related to cardiac complications. Half of the graft failures occurred within the first month; very few occurred after 12 months. The majority of amputations following graft failure were also carried out within the first month. Johnson *et al.*[26] identified a group consisting of 22 per cent of patients with critical ischaemia who underwent limb amputation following a failed limb salvage procedure and suggested that primary amputation may have been more cost effective. The present authors agree with Taylor *et al.*[9] that preserving limb function is a more important goal. In a previous series of patients who had arterial reconstruction for critical limb ischaemia, the mortality rate in this unit was 8 per cent at 30 days and 20 per cent at 12 months[27]. Graft patency was 96 per cent at 30 days and 83 per cent at 12 months. The majority of these procedures (93 per cent) were carried out under general and epidural anaesthesia. The present series comprised a selected high-risk group and it is not surprising that both survival and graft patency rates were significantly reduced compared with those in patients fit for general anaesthesia. Limb salvage rates in the present study, however, are consistent with those of other published series[3,4]. The use of local infiltration anaesthesia combined with simple regional nerve block may offer high-risk patients, who might be considered unfit for prolonged general anaesthesia, the opportunity of reconstruction rather than primary amputation.

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Efficacy and safety of enoxaparin *versus* unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment

ENOXACAN Study Group (see appendix)

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Background Surgery for malignant disease carries a high risk of deep vein thrombosis. The aim of this study was to evaluate the prophylactic effect of a low molecular weight heparin, enoxaparin, 40 mg once daily, beginning 2 h before surgery, compared with that of unfractionated low-dose heparin three times daily.

Methods Patients included were over 40 years of age and undergoing planned elective curative abdominal or pelvic surgery for cancer. The study was designed as a prospective double-blind randomized multicentre trial with participating departments from ten countries. Primary outcome was venous thromboembolism as detected by mandatory bilateral venography or pulmonary scintigraphy. Follow-up was at 3 months.

Results Some 1115 patients were randomized into the study but venograms were inadequate in 460 (41·3 per cent). Of 631 evaluable patients, a total of 104 (16·5 per cent) developed thromboembolic complications. The frequency was 18·2 per cent in the heparin group and 14·7 per cent in the enoxaparin group (95 per cent confidence interval of the difference −9·2–2·3 per cent). There were no differences in bleeding events or other complications. One patient in the heparin group developed severe thrombocytopenia. There were no differences in mortality at either 30 days or 3 months.

Conclusion Enoxaparin, 40 mg once daily, is as safe and effective as unfractionated heparin three times daily in preventing venous thromboembolism in patients undergoing major elective surgery for abdominal or pelvic malignancy.

In elective abdominal surgery, patients with malignant disease belong to a high-risk group for venous thromboembolic complications, comparable to patients having major orthopaedic surgery[1]. Patients with cancer have haemostatic abnormalities which predispose them to develop thrombosis[2]. Furthermore, patients with thrombosis have an increased risk of malignant disease[3]. The need for perioperative antithrombotic prophylaxis is agreed, although the choice of method may differ. Low molecular weight heparins (LMWHs) have been shown to be effective and safe for thromboprophylaxis[4–7]. A higher dosage of LMWH might be required to obtain adequate prophylaxis in patients with malignant disease. In a recent study of two dosages of the LMWH dalteparin, the higher dose (5000 anti-Xa units *versus* 2500 units, once daily) was significantly more effective in patients with cancer[8]. In a previous study, LMWH enoxaparin at a dose of 20 mg daily was less effective than unfractionated low-dose heparin (UFH) in patients with cancer, whereas it was effective in patients with benign disease[9]. A dose of 40–60 mg enoxaparin daily is effective prophylaxis in hip surgery[10–12].

The aim of this study was to evaluate the effect of enoxaparin 40 mg once daily, the first dose given 2 h before surgery, compared with that of UFH three times daily, for thromboprophylaxis in patients undergoing planned curative abdominal or pelvic surgery for cancer.

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Patients and methods

The study was designed as a prospective double-blind randomized multicentre trial. Consecutive patients aged 40 years or over scheduled for open elective curative surgery under general anaesthesia for abdominal or pelvic cancer (gastrointestinal, urological, gynaecological) were included. The following criteria were also required: the planned duration of surgery should exceed 45 min, postoperative hospitalization should be at least 6 days and the patient's expected survival should be at least 6 months. Exclusion criteria were renal or hepatic insufficiency, laparoscopic surgery, hypersensitivity to radiographic contrast media, heparin or LMWH, recent cerebrovascular thrombosis, haemorrhage, neurosurgery or known cerebral metastases, generalized bleeding disorder, endocarditis, active peptic ulcer, untreated arterial hypertension, deep vein thrombosis (DVT) and/or pulmonary embolism within 3 months, treatment with heparin, LMWH or an oral anticoagulant within 5 days, pregnancy or lactation. After operation some procedures were reclassified as palliative and some were explorations, shorter than 45 min. These patients were included in the analysis as they had been randomized.

Separate randomization was made per country and per hospital to one of two groups (1:1 ratio). (1) unfractionated heparin (UFH) 5000 units subcutaneously (0·2 ml) (Dupont-Pharma, Paris, France) – first injection 2 h before operation and then three times daily until venography on day 10 ± 2; the same UFH was used throughout the trial and in all centres; (2) enoxaparin 40 mg subcutaneously (0·2 ml) (Rhône-Poulence Rorer, Paris, France) – first injection 2 h before operation and then once daily until venography on day 10 ± 2; in this group, two placebo injections (0·2 ml) were given daily. Injections were given subcutaneously either in the lateral abdominal wall or in the thigh In each country, the drug was shipped to investigators in multiples of complete blocks.

Outcome measurements

The primary endpoint was the development of documented venous thromboembolism. Bilateral ascending venography was performed within 24 h after the last injection of the trial substance. If the patient developed clinical symptoms or signs of DVT, unilateral venography was performed within 24 h. If positive, the patient was considered to have reached an endpoint. If negative, the patient continued in the study and planned bilateral venography was performed.

For statistical analysis, the venographic results were evaluated and agreed on by an independent panel of two radiologists before the code was broken. The venogram was considered evaluable only when the entire deep venous system was visualized to the level of the common iliac vein. The following segments had to be assessed as 'adequately visualized' to consider the venogram adequate: external iliac, common femoral, superficial femoral, popliteal, posterior tibial (at least one branch) and peroneal (at least one branch). If any one of these segments was assessed inadequate, the whole venogram was classified inadequate, whether or not the other segments were adequately visualized, unless a thrombus was diagnosed. Patients with DVT in one leg and a contralateral unevaluable venogram were considered as having DVT. Those with one negative and one unevaluable venogram were classified as inadequately evaluated.

The venographic definition of DVT was a constant intraluminal filling defect seen in two projections. Thrombi in the popliteal vein or above were considered proximal, others being distal Whether or not the DVTs were symptomatic was recorded.

If pulmonary embolism was suspected clinically, a ventilation–perfusion lung scan and/or pulmonary angiography was performed. If a diagnosis of pulmonary embolism was established, the patient was considered to have reached an endpoint; if not, the planned bilateral venography was performed.

Haemorrhage was a second endpoint in the study. Blood loss was measured during and after operation, and transfusion requirements were reported. Bleeding from drains was measured daily, and injection site haematomas were noted. Bleeding complications occurring during and after operation were classified by the investigator as minor or major. Haemoglobin and platelet counts were measured before operation and on days 3, 4, 6, 8, 10 and 12 or until discharge. Any of the following events was considered as major: excessive peroperative bleeding, clinically overt bleeding with either a fall in haemoglobin concentration of 2 g/dl or more or the need for transfusion of at least 2 units of blood; intracranial, intraocular bleeding, retroperitoneal or any bleeding leading to reoperation or death; and, finally, any bleeding that necessitated stopping the trial medication.

Adverse events were compared between the two groups according to the Costart system[11]. All patients were followed up at 3 months (± 10 days) after operation. Death, venous thromboembolism and major haemorrhagic episodes were recorded during this interval. In case of death, autopsy was performed whenever possible. Cause of death, when there was no autopsy, was based on information in the case report form. This review was made before unblinding.

Statistical analysis

It was calculated that 400 eligible patients would be needed per group to have a power of 80 per cent to conclude that enoxaparin was no different from UFH by more than 6 per cent, assuming a true frequency of DVT of 10 per cent in both groups. Considering that about 20 per cent of the patients would not have venography and 15 per cent of venograms would be inadequate according to the expert reading, a total of 1150 patients was thought necessary to reach 800 for analysis. Confidence intervals were used in the estimation and interpretation of venous thromboembolism rates between the groups.

Efficacy analysis was made on an all treated patients basis as well as on the basis of evaluable patients, after exclusion according to the following criteria: patients without adequate endpoint assessment; patients who did not receive the preoperative dose or less than 80 per cent of the doses during the five postoperative days; when surgery was not performed or the planned procedure was not an elective curative procedure for cancer; concomitant treatment with heparin or dextran; second record for patients randomized twice.

Safety analysis was made on all treated patients.

Subgroup analyses were made for venous thromboembolism as follows: age (less than 60 years or 60 years and over), risk factors for DVT and pulmonary embolism, obesity (body mass index for males greater than 27·2, for females greater than 26·9), sex, type of surgery, duration of surgery (less than 4 h or 4 h and more), country, investigator.

Ethics

The study was performed according to the Declaration of Helsinki and good clinical practice. Regional ethics committees in the various countries approved the trial. Written informed consent was obtained from all patients.

Results

The 1116 patients were recruited between April 1993 and February 1995 by 34 investigators in ten countries; 560 were randomized to receive UFH and 556 enoxaparin. One patient randomized to enoxaparin did not receive any study medication at all and was excluded from further analysis. Adequate endpoint evaluation was not available in 460 patients. Six received insufficient prophylaxis according to the protocol and 18 received prohibited concomitant medication. The remainder had inadequate venograms. The evaluable patient population was 631 patients, 319 who received UFH and 312 enoxaparin. Demographic data and risk factors for DVT in evaluable patients are shown in *Table 1*; the groups were well matched.

Some 848 patients (76·0 per cent) were 60 years of age or older. Five patients were younger than 40 years. The four most common procedures were anterior resection (222), sigmoid resection (179), right hemicolectomy (156) and abdominoperineal resection (103). There were no differences between the two groups in the distribution of

Table 1 Demographic variables in all evaluable patients

	UFH (*n* = 319)	LMWH (*n* = 312)
Median (range) age (years)	68 (35–90)	69 (32–91)
Sex ratio (M:F)	167:152	166:146
Median (range) body mass index	24·8 (13·9–41·8)	24·3 (15·9–51·4)
History of venous thromboembolism*	13 (4·1)	7 (2·2)
Varicose veins*	62 (19·4)	49 (15·7)
Congestive heart failure*	30 (9·4)	33 (10·6)
Chronic pulmonary obstruction*	21 (6·6)	17 (5·4)
Prolonged immobilization before surgery (> 72 h)*	5 (1·6)	7 (2·2)
Oestrogen medication*	11 (3·4)	13 (4·2)

*Values in parentheses are percentages. UFH, unfractionated low-dose heparin; LMWH, low molecular weight heparin

Table 2 Venous thromboembolism in evaluable patients

	UFH ($n = 319$)	LMWH ($n = 312$)	95 per cent c.i. of the difference (%)	Conclusion
DVT only	56 (17·6)	45 (14·4)		
Pulmonary embolism* plus DVT	2 (0·6)	0 (0)		
Death†	0 (0)	1 (0·3)		
Total	58 (18·2)	46 (14·7)	−9·2–2·3	Equivalent

Values in parentheses are percentages. UFH, unfractionated low-dose heparin; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; c.i., confidence interval. *Scintigraphic verification (high probability); †considered thromboembolic

Table 3 Blood loss and haemorrhagic complications in 1115 treated patients

	UFH ($n = 560$)	LMWH ($n = 555$)
Median (range) intraoperative bleeding (ml)	500 (11–9670)	500 (22–7000)
Median (range) postoperative bleeding in drains (ml)	434 (2–11 250)	385 (2–6520)
Transfusion requirement*	242 (43·2)	284 (51·2)
Peroperative bleeding*	55 (9·8)	60 (10·8)
Major bleeding*	16 (2·9)	23 (4·1)
Minor bleeding*	80 (14·3)	81 (14·6)
Discontinuation of prophylaxis*	12 (2·1)	18 (3·2)
Injection site haematoma*	11 (2·0)	6 (1·1)
Decrease in first postoperative haemoglobin estimation of 20 g/l or more (from baseline)*	270 (48·2)	281 (50·6)

*Values in parentheses are percentages. UFH, unfractionated low-dose heparin; LMWH, low molecular weight heparin

these or any other types of surgery. The mean duration of operation was 2 h 59 min (range 23 min to 12 h 50 min) in the UFH group and 2 h 57 min (range 27 min to 9 h) in the enoxaparin group. Although the aim of surgery was curative, it was reclassified as palliative after operation in 149 patients (13·4 per cent), 77 in the UFH group and 72 in the enoxaparin group.

A total of 1086 patients (97·4 per cent) received the preoperative dose of prophylaxis. The median time lapse between this dose and surgery was no different between the two groups (2 h 30 min (range 0 min to 40 h)).

Some 104 (16·5 per cent) of the 631 evaluable patients developed postoperative venous thromboembolism, 58 in the UFH and 46 in the enoxaparin group (*Table 2*). The observed odds ratio was 0·78 (0·51–1·19). Of the 101 DVTs, ten were symptomatic (six and four in UFH and enoxaparin groups respectively). The two patients in the UFH group with pulmonary embolism had clinical symptoms with scintigraphic verification. In spite of the large number of failed venographies, equivalence was not rejected in the evaluable population.

There was no difference in the anatomical distribution of DVTs in evaluable patients. There were 51 distal (16·0 per cent) and six proximal (1·9 per cent) DVTs in the UFH group *versus* 42 (13·5 per cent) and three (1·00 per cent) in the enoxaparin group.

In the evaluable colorectal subgroup, 18·8 per cent developed DVT in the UFH group compared with 16·6 per cent in the enoxaparin group. In the subgroup analysis a better effect (*P* not significant) of enoxaparin was seen in patients whose operations lasted for 4 h or more (eight (7·8 per cent) of 102 in the enoxaparin group *versus* 16 (13·9 per cent) of 115 in the UFH group).

The incidence of haemorrhage was 17·1 per cent (96 of 560 patients) in the UFH group and 18·7 per cent (104 of 555) in the enoxaparin group (*Table 3*). There were no significant differences between the two prophylactic groups. Major haemorrhage was seen in 2·9 per cent (16 of 560) of patients receiving UFH and in 4·1 per cent (23 of 555) of those having enoxaparin (*P* not significant). Major haemorrhage occurred away from the operative site in seven patients in the UFH group and in nine in the enoxaparin group.

There were no differences between the two groups when adverse events were analysed according to the Costart classification.

In three patients receiving UFH and in one receiving enoxaparin, platelet count fell below 70 000 per μl. One UFH-treated patient had severe thrombocytopenia (less than 30 000 per μl), which developed on day 8. In the others the platelet count improved despite drug continuation.

At the 3-month follow-up, 13 patients were lost or information was missing. Sixty patients had died, 34 in the UFH group and 26 in the enoxaparin group. Seven and four deaths respectively occurred during the treatment period and 27 and 22 respectively during follow-up. Autopsy was performed in 17 per cent, the most frequent cause of death being cancer or its complications. Of these 60 deaths, nine were considered thromboembolic in origin: two during the treatment period (both in the enoxaparin group) and seven during follow-up (four in the UFH and three in the enoxaparin group). The basis for considering the deaths thromboembolic was autopsy findings in two, death after confirmed DVT in three, clinically significant symptoms of pulmonary embolism in two and sudden death in two. The overall 30-day mortality rate was 2·2 per cent (14 UFH, 11 enoxaparin).

Fifty-two patients had further surgery during follow-up (27 and 25 in the UFH and enoxaparin groups respectively).

Discussion

This large study of thromboprophylaxis in patients undergoing surgery for abdominal or pelvic cancer used mandatory bilateral venography to diagnose DVT. The criteria for an adequate venogram were very strict. As a result, data for 460 patients (41·2 per cent) were inadequate for interpretation, or not available as determined by the independent adjudication committee. However, there was no difference between the groups and, as the study was double-blind, there is no reason to believe that the non-evaluable patients would have differed in the frequency of DVT because of bias.

The investigation showed that the LMWH enoxaparin once daily was equivalent to UFH given three times daily for thromboprophylaxis in patients undergoing surgery for abdominal or pelvic cancer. In view of the many patients who completed the protocol ($n = 631$), the conclusion of an equivalent prophylactic effect is firm. In evaluable patients the odds ratio was 0·78 in favour of enoxaparin, a risk reduction compared with UFH similar to that shown in various meta-analyses[5–7]. This effect was obtained without decreasing safety or increasing bleeding or other complications.

Alternative methods for diagnosis of DVT with a higher compliance could have been the fibrinogen uptake test or colour-coded ultrasonography. When the study was initiated, the fibrinogen uptake test was, however, prohibited in most of the participating countries because of risk of viral transmission. The use of colour-coded ultrasonography has a low sensitivity in patients with asymptomatic DVT[14,15]. Venography was selected because it is the 'gold standard' in the diagnosis of DVT. Another advantage of venography is that the films can be evaluated by an independent committee. Although the frequency of symptomatic DVT was low, the overall incidence of DVT in evaluable patients in this study (16·5 per cent) was clearly demonstrated by venography.

Within the group of patients having abdominal surgery, this study dealt with high-risk patients[16]. Most previous studies have included fewer patients with malignancy. The aim of this study was to include patients in whom surgery was planned to be curative. However, 13·4 per cent of the patients were found at surgery to have an incurable tumour and underwent a palliative procedure. Once randomized they were, however, kept in the study.

The frequency of DVT in evaluable patients who received enoxaparin (14·7 per cent) could be compared with a recent dalteparin study where the frequency in patients with cancer receiving 5000 XaI units was reported as 9 per cent using the fibrinogen uptake test[8]. Thus, even with prophylaxis, patients having surgery for cancer have a high risk of DVT and there is a clear need for further improvement in prophylactic methods. This could include increased doses of LMWHs, combination with mechanical methods, or new modalities. A similar incidence of DVT was found in patients with cancer in the Canadian Colorectal DVT Prophylaxis Trial where bilateral venography was also used for efficacy assessment (15 per cent)[17] and in a smaller Norwegian study (12 per cent)[18].

This study differs from most others in the large number of centres involved from many countries and also from several continents. There were variations in results, but the main conclusions on efficacy and safety were not altered. A potential advantage of a multicentre study is its generalizability.

Scurr *et al.*[19], and subsequently others[20,21], have called attention to the high rate of thromboembolism following discharge after high-risk surgery. The frequency at 3 months of clinically relevant thromboembolic complications with objective verification after discharge was low in this study (1·8 per cent), in accordance with the findings of Kakkar *et al.*[22]. In elective hip surgery there are indications that prolonged prophylaxis is beneficial[20,21]. Whether this is also true for abdominal cancer surgery is not known, but judging from the data in this study the risk seems low.

The incidence of major bleeding complications did not differ between the groups and was similar to that in other recent studies[8,22]. There were no intracranial or intraocular haemorrhages. Thrombocytopenia occurred in only one patient in the UFH group. Both regimens used in this study were safe.

In conclusion, enoxaparin in a dose of 40 mg once daily is at least as effective and safe as UFH three times daily in preventing postoperative thromboembolism in patients having surgery for abdominal and pelvic malignancy.

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Appendix

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Early effect of carotid endarterectomy on arterial blood pressure measured with an ambulatory monitor

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Background Carotid artery disease and hypertension are associated, and carotid endarterectomy is often followed by acute changes in blood pressure. As the carotid sinus is responsible for short-term blood pressure control, occlusive carotid disease may contribute to the mechanism of preoperative hypertension.

Methods Ten patients undergoing carotid endarterectomy and eight having a peripheral bypass procedure were studied 2 weeks before and 2 weeks after operation, using home ambulatory blood pressure measurement.

Results A significant fall in both mean systolic (−14·4 mmHg) and mean diastolic (−12·7 mmHg) pressure was observed after carotid endarterectomy ($P < 0{\cdot}006$), whereas no change was seen in controls.

Conclusion These results suggest that there is an increase in carotid sinus activity in patients following carotid endarterectomy and supports the hypothesis that carotid sinus dysfunction contributes to hypertension in patients with carotid artery disease.

Since the report by Eastcott *et al.*[1] of successful surgery for symptomatic carotid artery disease, carotid endarterectomy has become an accepted treatment for transient ischaemic attacks and strokes[2]. Both the North American Symptomatic Carotid Endarterectomy Trial[3] and the Medical Research Council's European Carotid Surgery Trial[4] concluded that the benefits of the operation outweigh the risks in symptomatic patients with carotid artery stenosis greater than 70 per cent of the vessel diameter. There are well known associations between stroke, hypertension and occlusive carotid disease[5–7], but whether hypertension is causally related to occlusive carotid artery disease or is an epiphenomenon is still not clear. The immediate effect of carotid endarterectomy on blood pressure is well recognized[8–10], but appears to be temporary[11–13]. The acute postoperative hypertension observed in some patients has been attributed to carotid sinus nerve damage and has led to a recommendation that the carotid sinus nerve should be preserved[14]. Conversely, postoperative hypotension has been attributed to an increase in carotid sinus reflex activity as it can be controlled by instillation of local anaesthetic until secondary adaptation occurs[9]. The medium-term effect of carotid endarterectomy on blood pressure is not known.

Single blood pressure measurements using a sphygmomanometer are unreliable, particularly in hypertensive patients, and ambulatory blood pressure monitoring has been shown to give more reliable estimates of the true mean systolic and diastolic pressures[15]. The aim of this study was to use home ambulatory blood pressure monitoring to see whether there is a clinically significant change in mean systolic and diastolic blood pressure early after carotid endarterectomy.

Patients and methods

After obtaining local ethics committee approval, indirect brachial artery blood pressure measurements were made using a portable ambulatory blood pressure monitor (Oxford Instruments, Oxford, UK) over a 15-h waking interval between 07.00 and 22.00 hours in three groups of subjects: (1) young normotensive controls, (2) patients undergoing a peripheral vascular bypass procedure (e g femoropopliteal bypass); and (3) patients undergoing carotid endarterectomy. The diagnosis of significant carotid artery disease was made using duplex ultrasonography augmented with digital subtraction angiography in selected cases[16]. The ambulatory monitor was fitted to each subject at home and programmed to take measurements at random intervals of around 15 min, allowing up to 60 measurements. Two recordings were made at home 4 weeks apart (2 weeks before and 2 weeks after operation in groups 2 and 3). This was done to ensure similar levels of mobility, to minimize the effect of stress from hospital treatment and to allow any acute perioperative changes in blood pressure to settle. No changes were made to the treatment of patients already on antihypertensive medication All patients had carotid endarterectomy under general anaesthesia; the carotid sinus nerve was preserved where possible but infiltrated with local anaesthetic solution during the operation.

Study design

The reproducibility of the ambulatory blood pressure measurement was determined with the normal subjects (group 1) and the results were used to estimate the number of patients required (groups 2 and 3) for a change in mean systolic or diastolic pressure of 10 mmHg to be significant at the 5 per cent level using the standard power formula:

$$n > 2\left(\frac{z_{2\alpha}\sigma}{d_1}\right)^2$$

where n is the required number in the sample, 2α is the required two-sided significance level ($2\alpha = 0{\cdot}05$), σ is the estimated standard deviation of the sample and d_1 is the required difference in the means.

Statistical analysis

Assuming an approximately normal distribution of both mean systolic and mean diastolic blood pressures, an unequal variance t test was used to compare differences between the groups, and a paired t test to compare changes in blood pressure within the groups. The threshold for statistical significance was taken as $P = 0{\cdot}05$

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Results

The results of the ambulatory measurements in the young normotensive group (group 1, $n=6$) are shown in *Table 1*. There was no statistically significant difference between the mean systolic pressure ($t=-1{\cdot}37$, 5 d.f., $P=0{\cdot}23$) or the mean diastolic pressure ($t=-0{\cdot}05$, 5 d.f., $P=0{\cdot}96$) measured over the 4-week interval. The sample variation of the mean systolic and diastolic pressures indicated that, using ambulatory blood pressure monitoring, at least seven subjects would be required to show a change in mean diastolic or systolic pressure of 10 mmHg.

The median number of blood pressure recordings of at least 40 in all groups indicates that the ambulatory monitor is reliable and well tolerated. The small difference in both the mean systolic and diastolic pressures measured in the young normotensive subjects shows that the ambulatory measurement technique provides a sufficiently accurate estimate of the mean systolic and diastolic pressures.

The blood pressure measurements for the 18 patients who had arterial surgery are shown in *Table 2*. Patients who had carotid endarterectomy (group 3, $n=10$) were well matched for age and sex with those having a peripheral artery bypass (group 2, $n=8$). Before operation, patients who had carotid endarterectomy had a significantly higher mean systolic ($t=2{\cdot}35$, 14 d.f., $P=0{\cdot}03$) and mean diastolic ($t=2{\cdot}65$, 14 d.f., $P=0{\cdot}02$) pressure than those who underwent peripheral artery bypass, despite being on antihypertensive therapy.

Patients having carotid endarterectomy showed a significant fall in both mean systolic ($t=3{\cdot}54$, 9 d.f., $P=0{\cdot}006$) and mean diastolic ($t=5{\cdot}11$, 9 d.f., $P=0{\cdot}0006$) pressure, whereas there was no significant change in either mean systolic ($t=0{\cdot}57$, 7 d.f., $P=0{\cdot}6$) or mean diastolic ($t=-0{\cdot}51$, 7 d.f., $P=0{\cdot}62$) pressure following a peripheral bypass operation.

Table 1 Reproducibility of ambulatory blood pressure recording in young normotensive subjects (group 1)

	Group 1
No of subjects	6
Median no. of blood pressure readings per subject	44
Mean age (years)	22
Sex ratio (M:F)	4:2
No with hypertension	0
Mean(s.d.) blood pressure (mmHg)	
Systolic I	111·6(8·4)
Diastolic I	69·7(10·7)
Systolic II	113·2(9·3)
Diastolic II	69·8(7·6)
Change in systolic pressure	1·6(2·8)
Change in diastolic pressure	0·1(3·5)

Measurements were made on two occasions (I, II) with an interval of 4 weeks

Table 2 Ambulatory blood pressure recordings made 2 weeks before and 2 weeks after operation in patients who had a peripheral artery bypass (group 2) or carotid endarterectomy (group 3)

	Group 2	Group 3
No of subjects	8	10
Median no of blood pressure readings per subject	40	44
Mean age (years)	69·1	70·3
Sex ratio (M:F)	5·3	7·3
No. with hypertension	5	9
Mean(s.d.) blood pressure (mmHg)		
Preop. systolic	111·9(11·8)	124·5(10·6)
Preop. diastolic	68·2(6·8)	80·6(12·8)
Postop. systolic	111·1(13·7)	110·1(10·6)
Postop diastolic	69·1(8·3)	67·9(7·0)
Change in systolic pressure	−0·8(4·4)	−14·4(12·9)
Change in diastolic pressure	0·8(4·8)	−12·7(7·9)

Discussion

Inzitari *et al.*[17] reported that systolic hypertension was a better predictor of the extent and severity of extracranial disease than age. Van Merode *et al.*[18] showed an association between hypertension and peripheral vascular disease in screened asymptomatic men (50–69 years old) and Lusiani and co-workers[6] found an increase in the prevalence of internal carotid artery disease in hypertensive patients compared with an age- and sex-matched group of normotensive subjects. These observations show a strong association between hypertension and arterial disease, particularly carotid artery disease, but do not prove that hypertension causes arterial disease, or vice versa.

Hypertension is associated with a decrease in baroreceptor sensitivity[19] which is independent of the fall in baroreceptor sensitivity with age[20]. Takeshita *et al.*[21] demonstrated reduced baroreceptor sensitivity in young, borderline, hypertensive subjects and a post-mortem study by Winson and colleagues[22] showed a progressive reduction in the distensibility of both the carotid artery and carotid sinus with age. However, van Merode *et al.*[23] showed reduced carotid compliance in both young and elderly hypertensive subjects compared with normotensive controls, which suggests that the decreased carotid sinus sensitivity associated with hypertension may be secondary to early loss of carotid artery compliance. Animal studies have shown that baroreceptor denervation results in an initial rise in mean blood pressure which recovers over several days, together with an increase in blood pressure variability which is more permanent[24]. In addition, McCubbin[25] showed that the baroreceptor reflex is reset in chronic hypertension such that it maintains, rather than opposes, the increase in blood pressure. These observations suggest that the baroreceptor reflex is important in the short-term regulation of blood pressure by damping acute increases in blood pressure caused by other physiological mechanisms. A reduction in carotid sinus sensitivity may therefore contribute to the development of established hypertension by loss of the normal blood pressure buffering function and subsequent resetting of the baroreceptor reflex.

The definition of hypertension is largely empirical and depends on the method used to measure blood pressure. High beat-to-beat variability, especially in borderline hypertensive patients and in stressful situations, means that isolated measurements are unreliable for assessing changes in individual patients. Accurate measurement of blood pressure ideally requires continuous invasive recording over an extended time interval. While continuous intra-arterial measurement is possible in hospital, it is not feasible for outpatient studies. Di Rienzo *et al.*[26] showed that intra-arterial blood pressure measured in ambulant hypertensive patients gave an accurate estimate of the mean 24-h pressure only if 40 evenly spaced samples were used. Making this many recordings in ambulant outpatients has been practical only since the development of portable, miniaturized, automatic blood pressure recorders in the early 1980s[27].

The present observation of significant falls in both mean systolic and diastolic blood pressure measured in ambulant outpatients after carotid endarterectomy supports the hypothesis that occlusive carotid disease in the region of the carotid sinus reduces its sensitivity to changes in pressure. One mechanism that has been proposed to explain this is a decrease in the distensibility of the carotid sinus caused by atheroma[28]; however, Angell-James and Lumley[9] showed a decrease in carotid sinus distensibility as a result of carotid endarterectomy. These apparently contradictory observations become consistent if the haemodynamic effect of the carotid stenosis is considered.

The presence of significant stenosis causes a jet of blood which results in a reduced lateral pressure within, and immediately downstream of, the stenosis (Venturi effect). The reduced lateral pressure would cause less distension of the carotid sinus and reduce its sensitivity. Removal of the atheroma at operation would eliminate this Venturi effect and expose the wall of the carotid sinus to a higher lateral pressure, resulting in the dilatation, stiffening and increase in reflex activity observed by Angell-James and Lumley[9]. The increased luminal diameter would, according to the law of Laplace, also act to increase the tension in the wall of the carotid sinus. Local anaesthetic blockade of the carotid sinus nerve lasts only for several hours[9] and if the carotid sinus nerve were damaged during operation there would be no reflex hypotension; instead a hypertensive response might be predicted, the degree of which would depend on the preoperative residual activity of the carotid sinus reflex. Thus, the combination of changes in carotid sinus haemodynamics, wall mechanics and nerve function could explain the variable blood pressure response following carotid endarterectomy. This proposed mechanism supports the hypothesis that carotid artery atheroma contributes to the high prevalence of hypertension in these patients by reducing carotid sinus sensitivity and the reflex damping of normal blood pressure variations.

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Claudication distance is poorly estimated and inappropriately measured

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Background Claudication distance is the commonest measure of the disability caused by lower-limb occlusive arterial disease. The accuracy of claudication distance as a surrogate for handicap has been assessed.

Methods Seventy patients who attended a specialist vascular clinic with intermittent claudication were studied prospectively. Patients were asked to estimate their claudication distance and maximum walking distance before undergoing both a patient-controlled corridor walk and a fixed-speed treadmill walk.

Results The claudication distance reported by patients bore little relation to the distance recorded in the medical correspondence. There was no correlation between the estimated distance and the actual distance walked on either a patient-controlled corridor walk or a fixed-speed treadmill walk. Most patients were able to walk substantially further at their own speed on the corridor than on the treadmill at a slower speed.

Conclusion Claudication distance is spuriously estimated, inaccurately reported, falsely recorded, inappropriately measured and usually misinterpreted. It is of little value in judging the need for treatment. Objective measures of the handicap caused by the disability of reduced walking distance are required if rational management decisions are to be made.

The assessment of patients with intermittent claudication requires evaluation of both disability and handicap. Reduced walking distance is a disability that causes a handicap only if it interferes with the patient's usual activities. The same disability that substantially handicaps an active patient may barely be noticed by a less active person. For example, a person aged 75 years who can walk only 50 m, but who has no inclination or need to walk more than 50 m, has a substantial disability, but no handicap[1].

Intervention for intermittent claudication may be indicated for those handicapped by their disability but not in those without handicap. The distinction between disability and handicap is important, but handicap is difficult to quantify whereas disability is measured easily. The disability of claudication is expressed as claudication distance (the distance walked before the onset of pain) or maximum walking distance (MWD) (the distance walked before ischaemic muscle pain becomes unbearable).

The aim was to evaluate claudication distance and MWD, as stated by the patient, as recorded by the referring doctor and the vascular specialist, and as measured objectively on a patient-controlled corridor walk and a fixed-speed level treadmill walk.

Patients and methods

Seventy patients referred over 6 months to the Oxford Regional Vascular Service with intermittent claudication were studied. Patients with rest pain or ulceration were excluded, but those with night pain and claudication were included. The referral letters and subsequent clinic letters were analysed, and the recorded claudication distance and handicap noted. In addition, patients were asked to estimate the distance at which they first experienced pain (claudication distance) while walking, the furthest distance they could walk (MWD) and the time taken to walk these distances.

Patients were asked to walk at their normal pace up and down a ward corridor without stopping, and to indicate when they first experienced pain (claudication distance) but to walk on until they could go no further (MWD). The length of the corridor was 30 m and the actual claudication distance and MWD were measured. Each corridor length of the walk was timed and a mean speed calculated; the median speed, the middle value of the mean speeds, was also recorded. When they said they could walk no further they were led immediately to a rest room 15–45 m away and a note was made of whether they were able to walk there without rest; in this way the veracity of the MWD was checked. Following a rest of at least 30 min, patients were then walked on a horizontal treadmill (Powerjog E-10; Sport Engineering, Birmingham, UK) at 3 km/h (or slower if they could not manage this) and their claudication distance, MWD and the corresponding times were recorded. On both corridor and treadmill, patients were stopped at 800 m.

Results

Seventy patients with claudication were evaluated; 52 were men (74 per cent) and the median age was 69 (range 41–84) years. From their history and appearance on the corridor walk, five patients were further assessed and found to have a neurological cause for the claudication, either spinal stenosis (two patients) or nerve root entrapment (two) confirmed by magnetic resonance imaging, or a spastic myopathy as part of a postviral syndrome (one). These five were discounted from the walking analyses.

Some 54 per cent of referral letters and 83 per cent of clinic replies attempted to quantify disability in terms of claudication distance or MWD, whereas only 20 and 24 per cent respectively mentioned how the disability handicapped the patient. There was little correlation between the distance given by the patient at the time of the walking assessment and the distance recorded in the

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correspondence by either the referring practitioner ($r = 0{\cdot}45$) or the vascular specialist ($r = 0{\cdot}44$). In the 38 referral letters that did quote a distance, 27 gave a shorter distance (claudication distance or MWD) than the patient. Distances recorded in the clinic letter correlated better with the referral letter ($r = 0{\cdot}7$).

Only 30 patients were able to give an estimate of the length of time they were able to walk before they experienced pain (claudication distance). By contrast all could estimate a distance they were able to walk before pain; half (35 patients) said that they stopped as soon as they felt pain. There was no correlation between the claudication distance or MWD estimated by patients and the actual distance they walked on the corridor ($r = 0{\cdot}38$ for claudication distance, $r = 0{\cdot}47$ for MWD) (*Figs 1* and *2*) or on the treadmill ($r = 0{\cdot}34$ for claudication distance, $r = 0{\cdot}35$ for MWD).

The objective difference between the treadmill test and the corridor test was the patient's walking speed. Patients' initial corridor walking speed varied from 2 to 6·6 (median 4·6) km/h. The treadmill was maintained at 3 km/h. Fourteen patients (22 per cent) had a median corridor speed of less than 3 km/h, although only eight of these could not walk at 3 km/h on the treadmill. Two other patients whose median corridor lap speed was faster than 3 km/h could not keep up with the treadmill running at 3 km/h. Excluding these ten patients, who were tested at less than 3 km/h on the treadmill, 73 per cent of the remainder had a shorter claudication distance (76 per cent for MWD) on the treadmill than the corridor (*Figs 3* and *4*). Seventeen patients had been on a treadmill before (usually for assessment of coronary artery disease). The correlation between corridor and treadmill claudication distances in these patients was better ($r = 0{\cdot}84$ *versus* $r = 0{\cdot}64$), although they still walked further on the corridor.

Measurement of corridor lap times allowed the mean speed per lap to be calculated, and from this the median lap speed. There was a slight negative correlation between initial walking speed and age ($r = -0{\cdot}43$). There was no correlation between initial speed and claudication distance or MWD. Graphs of lap speed against distance walked were plotted. *Fig. 5* shows an example for five patients who experienced pain between 100 and 110 m on the corridor. The graph depicts the two strategies that patients employed to cope with the problem. Patients in

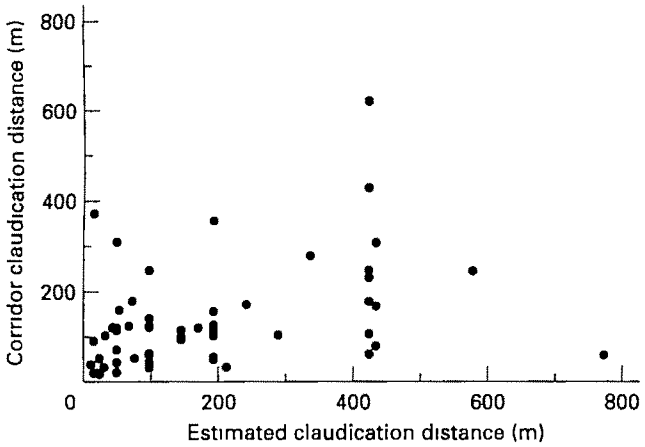

Fig. 1 Estimated and actual claudication distance measured on corridor walk

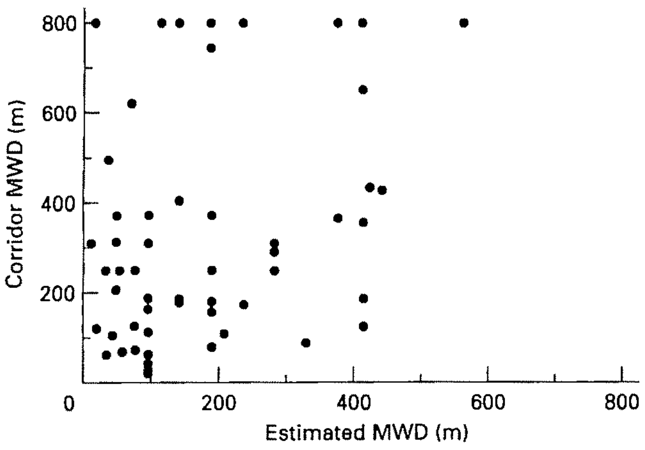

Fig. 2 Estimated and actual maximum walking distance (MWD) measured on corridor walk

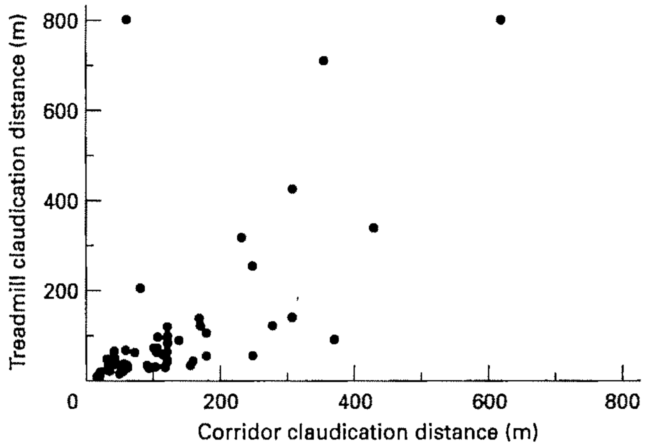

Fig. 3 Corridor and treadmill claudication distance. Most patients walk much further on the corridor before getting pain than on the treadmill, even though the treadmill is slower

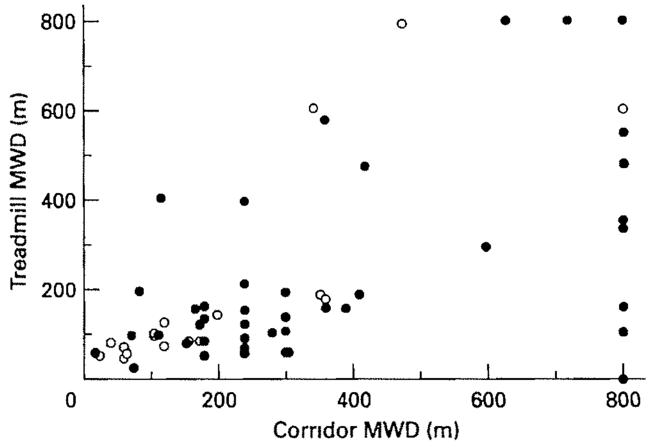

Fig. 4 Relation between maximum walking distance (MWD) on the treadmill and on the corridor. Most patients walk much further on the corridor than on the treadmill, even though the treadmill is slower. ○, Patients who walked straight back to the rest room; ●, patients who could walk no further

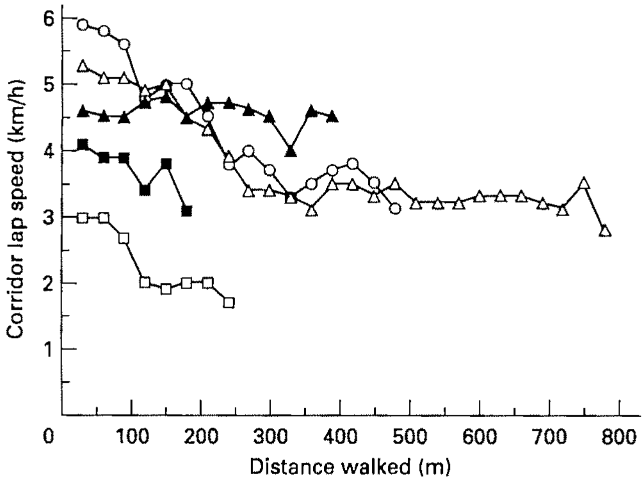

Fig. 5 Change in corridor walking speed with claudication The walking speeds of the five patients in the study who claudicated between 100 and 110 m are demonstrated as examples. Open symbols depict three patients who coped with their pain by slowing down and continuing to walk a little further. The closed symbols represent two patients who pressed on at full steam without slowing, and who came to an abrupt halt

one group slowed down and were then able to walk further with the pain, and in the case of one patient (△) the pain disappeared. Patients in the other group continued to walk at their normal speed before stopping and saying they could walk no further.

Fifteen (23 per cent) of 65 patients had a MWD greater than 800 m on the corridor. Fifty patients stopped at what they claimed to be their MWD, although 66 per cent of these were able immediately to walk a further 15–45 m back to the rest room.

Discussion

The assessment of handicap in patients with claudication is fundamental to their treatment because alleviation of handicap is the objective of revascularization by surgery or angioplasty. Handicap is more difficult to assess than disability, for which the measurement of walking distance is a proxy. Clinical signs of occlusive arterial disease, such as the absence or weakness of peripheral pulses, can readily be assessed in the clinic, and the ankle:brachial pressure index (ABPI) measured. Angiography can demonstrate the anatomy of the arterial tree, but does not indicate disability. Disability can be assessed directly by measuring the distance a patient can walk. Assessment has routinely used a motorized treadmill[2,3], but the measure of disability it provides is artificial.

Limitations of the treadmill were reported early, and have subsequently been studied in detail, including the learning curve[4], a phenomenon suggested in this study by the better performance of patients who had previously walked on a treadmill. Treadmill claudication distance has been shown to bear little relation to a patient's subjective estimate, irrespective of treadmill speed[5]. In spite of its limitations, the treadmill has been used to study the effects of various parameters on claudication distance, such as speed and incline[6], weight[7] and the effect of stopping smoking[8]. Treadmill testing has also been used for follow-up to determine change in claudication distance and MWD. It undoubtedly has a role in the diagnosis of vascular insufficiency in doubtful cases, when it should be combined with measurement of ABPI before and after exercise.

Differences in nature of the terrain, length of stride, ambient temperature, footwear and psychological factors may account for the inaccuracy of treadmill claudication. Some of the criticisms of treadmill assessment can also be levied at the corridor assessment described here, but corridor walking has the advantage that patients walk at their own speed, which can vary according to symptoms. Walking on the corridor is not a learned art, and does not involve noise and intimidating machinery. Recording the speed gives an insight into how patients cope with their disability (*Fig. 5*), either stopping immediately symptoms occur or persevering at a slower speed. The psychology involved when walking with pain was highlighted by the two-thirds of patients who said they could walk no further but then immediately walked 15–45 m to the rest room. This observation might differentiate between patients who would benefit from a programme of supervised exercise therapy[9] and those who already push themselves to their limit.

Claudication is the commonest symptom of vascular disease. A distinction should be made between the disability it causes and the resultant handicap, because treatment is appropriate only where significant handicap exists. The validity of patient estimates and treadmill measurements of claudication distance and MWD are questionable. In a typical case, a patient who is able to walk 300 m on the corridor (MWD) underestimates the walking distance to be 130 m. The referral letter under-reports the estimate as 60 m, and the vascular surgeon's perception of distance magnifies both errors. The cumulative distortions may be confirmed if a treadmill is used as a substitute for a measured real-terrain walking test. A patient could be offered intervention for a disability that may in fact be of no handicap whatsoever.

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Prospective randomized placebo-controlled trial of aprotinin for elective aortic reconstruction

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Background The serine protease antagonist, aprotinin, reduces perioperative blood loss in cardiac surgery and orthotopic liver transplantation. A pilot study suggested that the drug may also reduce bleeding during infrarenal aortic replacement; the aim was to confirm or refute this observation with a prospective, randomized, double-blind, placebo-controlled trial.

Methods Some 136 patients were randomized to receive either aprotinin, given as a loading dose of 2×10^6 kallikrein inactivator (KI) units followed by $0{\cdot}5 \times 10^6$ KI units/h or equal volumes of 0·9 per cent saline. After 80 patients had been randomized the infusion dose was doubled to ensure that plasma levels were similar to those seen in successful cardiac studies. Blood loss, coagulation and haematological parameters were recorded throughout surgery and for 7 days afterwards. Blood was transfused to maintain the haemoglobin level at 100 g/l.

Results Four patients were withdrawn after randomization when found at laparotomy to be unsuitable for the planned reconstruction. The 30-day mortality rate was 4·5 per cent, with no excess complications in either group. Blood loss collected on swabs was reduced from 480 ml in placebo-treated patients to 379 ml with aprotinin ($P = 0{\cdot}014$). Blood loss into suction drains in the first 24 h after operation was reduced from 295 to 205 ml in aprotinin-treated patients ($P = 0{\cdot}002$). However, no significant reduction was found in intraoperative or total blood loss, or transfusion requirement.

Conclusion The small reduction in blood loss in patients treated with aprotinin demonstrated in this study does not support its use in routine elective aortic surgery.

The serine protease inhibitor, aprotinin, was first used during cardiac surgery in the early 1960s when it was believed that excessive postoperative bleeding was due to increased plasma fibrinolysis. Tice and others[1,2] demonstrated that although aprotinin significantly reduced the fibrinolytic activity it had no effect on bleeding. In the late 1980s further studies demonstrated that high doses of aprotinin did significantly reduce blood loss during cardiac surgery[3–6]. The effect was more marked in patients undergoing revision surgery and in those previously treated with aspirin[7,8]. The mechanism of action of aprotinin centres around stabilization of platelet membrane glycoproteins which avoids inappropriate platelet activation and reduction of neutrophil activation[9].

Elective aortic reconstruction has many similarities to cardiac surgery; exposure of blood to foreign surfaces in prosthetic grafts, shear stresses resulting in platelet and white cell activation, and shifts in haemostatic balance caused by heparin, protamine and substituted blood, lead to the consumption of clotting factors and activation of the fibrinolytic system. Platelet sequestration, aggregation and activation also occur. In a pilot study, ten consecutive patients having an elective aortic reconstruction were given a loading dose of aprotinin of 2×10^6 kallekrein inactivator (KI) units followed by a continuous maintenance infusion[10]. The treated group was compared with 21 consecutive historical controls, well matched for age, sex, weight, risk factors and type of operation. Peroperative blood loss, intraoperative blood transfusion and postoperative blood loss were reduced significantly. On the basis of this study a prospective randomized placebo-controlled trial was organized to test the hypothesis that for patients undergoing elective aortic reconstruction the use of high-dose aprotinin could reduce blood loss and transfusion requirements.

Patients and methods

Ethics committee approval was obtained and patients gave informed consent for the trial. A consecutive series of 136 patients having elective aortic surgery were recruited. Patients were excluded if there was a history of previous exposure to aprotinin, hepatic or renal impairment, or if any antiplatelet agents had been taken during the preceding week. Randomization, in groups of four, was blinded from the investigators by the use of identical coded bottles containing active drug or placebo (0 9 per cent saline).

The aprotinin doses employed in the pilot study[10], determined from successful cardiac studies, were used again. A 5-ml test dose of either aprotinin 50 000 KI units or placebo was administered before the induction of anaesthesia in case of allergy. Subsequently 2×10^6 KI units aprotinin (200 ml) or an equal volume of placebo was given as a loading dose over 20 min, followed by a maintenance infusion of $0{\cdot}5 \times 10^6$ KI units/h or 50 ml/h placebo. After 80 patients had been randomized an independent analysis of the plasma levels achieved, without the investigators receiving code-breaking information, suggested that the maintenance infusion dose should be increased to 1×10^6 KI units/h in an effort to ensure that plasma levels were similar to those observed in cardiac studies.

Surgery was performed by either one of two consultants or a supervised senior registrar. Unfractionated heparin 2 mg/kg was given before aortic cross-clamping with milligram for milligram

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protamine reversal on completion. Blood samples for coagulation and haematological studies were taken from arterial or central venous lines before administration of the test dose, following induction of anaesthesia, 1 and 30 min after heparin administration, 1 min after protamine administration and then at 6 h, 24 h and 1 week after operation.

Swabs were weighed and the volume of blood lost was calculated. Blood collected into the suction canisters was recorded at the end of the procedure. A single 18-Fr suction drain was placed beside the aortic section of each graft with separate 14-Fr drains to each distal anastomosis of bifurcated grafts Losses were recorded separately for time intervals ending at 6, 12 and 24 h, and 1 week, or at drain removal. Blood transfusion was given when the haemoglobin level fell below 100 g/l measured on the theatre arterial blood gas analyser. All patients were monitored for at least the first 24 h following surgery in a high-dependency unit. Patients surviving to the first week were included in the primary data analysis but clinical follow-up continued to the 30th day.

Statistical analysis was by Student's *t* test for normally distributed data and Mann–Whitney analysis for non-parametric results. χ^2 analysis was used where excessive ties arose in non-parametric data.

Results

Some 136 patients were randomized. Four deaths occurred within 7 days of surgery (two in each group): one following massive haemorrhage, two from myocardial infarction and one from a pulmonary embolus. Four patients were found at operation not to be suitable for the planned reconstructive surgery: two had inflammatory aneurysms, one had unsuspected disseminated malignancy and one had a calcified aorta that could not safely be cross-clamped. These patients did not complete the protocol and are not considered in the subsequent analysis. Sixty-six patients received aprotinin and 62 placebo. The groups were comparable for age, sex, height, weight, disease process, operation type, duration of surgery and surgeon; no significant differences were found (*Table 1*).

Blood collected on to swabs, that which accumulated in the sucker bottle and postoperative drain loss were compared. Totals were calculated for intraoperative loss, postoperative loss to 24 h and total loss to 24 h. Swab loss was reduced from a median of 480 (range 149–1339) to 379 (range 35–1271) ml for patients treated with aprotinin ($z = 2{\cdot}208$, $P = 0{\cdot}014$; Mann–Whitney *U* test). Similar effects were observed for postoperative loss in the first 6 h and the first 24 h (*Fig 1*). However, no other measure of blood loss was reduced by aprotinin for the whole groups taken together (*Table 2*).

Aprotinin-treated patients received a mean of 2·2 (range 1–12, median 2) units of blood, compared with 1·9 (range 1–7, median 2) units for control patients. No differences were observed between the aprotinin- and placebo-treated patients for transfusion requirements after operation or for the total amount of blood transfused (*Table 3*).

Aprotinin cannot be expected to affect 'surgical' bleeding. The data were reanalysed, excluding patients with excessive blood loss, which included any patient with blood loss of more than 750 ml on to the swabs, 2000 ml collected into the suction drain or who had a total intraoperative loss of more than 2500 ml. Patients who experienced postoperative bleeding in excess of 1000 ml were also excluded. Eighteen of 66 patients treated with aprotinin and 11 of 62 control patients were removed from the data set, but no new effects were observed between the groups for either blood loss or transfusion requirement. The reduction of blood loss on to swabs in

Table 1 Comparison of aprotinin- and placebo-treated groups

	Aprotinin	Placebo	Value	*P*
No. of patients	66	62	0·72	0 40*
Sex ratio (M:F)	55·11	45:17	0 20	0·66*
Median age (years)	68	70	0·41	0·67†
Median weight (kg)	72	71	0·19	0·85†
Median height (m)	173	173	0·45	0·33‡
Disease				
Aneurysm	35	25	0·52	0·92*
Occlusive	17	20		
Mixed	13	15		
Inflammatory	1	2		
Median duration of operation (min)	100	104	0 13	0·45‡
Type of operation				
Tube graft	20	17	0·85	0·65*
Bifurcated graft	43	43		
Endarterectomy	3	2		
Surgeon				
1	9	5	0·54	0·76*
2	12	14		
3	45	43		

*χ^2 test;† Student's *t* test, ‡Mann–Whitney *U* test

Table 2 Comparison of blood loss in the 66 aprotinin-treated and 62 control patients

	Blood loss (ml)			
	Aprotinin	Control	*z**	*P**
Intraoperative				
Swabs	379·0 (251·5–561·5)	480·5 (353·3–659·3)	2·208	0 014
Sucker	800·0 (500·0–1400·0)	750·0 (418 8–1175 0)	0·982	n s.
Postoperative				
0–6 h	100·0 (50·0–167·5)	210·0 (117·5–295·0)	3 769	0·0001
6–12 h	57·5 (20·0–117·5)	50 0 (30·0–90·0)	0·205	n.s.
12–24 h	40·0 (20·0–78·8)	40·0 (20·0–70·0)	0·079	n.s.
>24 h	45·0 (0–140 0)	22·5 (0–90·0)	0·849	n.s.
Summary				
Intraoperative	1277·5 (833·5–1948 0)	1251 0 (924·8–1732·0)	0 296	n.s.
<24 h	205 0 (150·0–318·8)	295·0 (210 0–490·0)	2·830	0·002
Total	1555·0 (1061·8–2533·3)	1552·5 (1128·0–2195·3)	0·010	n.s.

Values are median (interquartile range) *Mann–Whitney *U* test; n.s , not significant

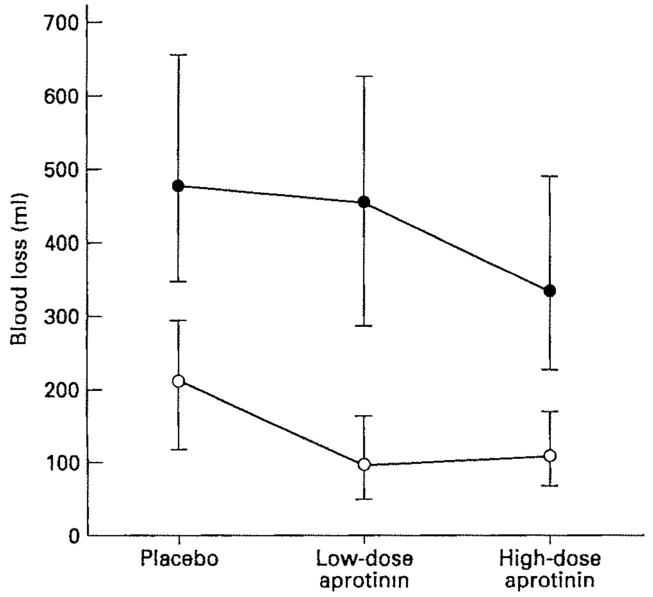

Fig. 1 Total blood loss in the first 24 h on swabs (●) and in suction drains (○) in patients treated with placebo, low-dose ($0·5 \times 10^6$ kallikrein inactivator (KI) units) and high-dose ($1·0 \times 10^6$ KI units) aprotinin Values are median (interquartile range)

Table 3 Number of units of blood transfused in 66 aprotinin-treated and 62 control patients

Transfusion period	No. of units Aprotinin	Control
Intraoperative	2 (0–4)	1 (0–4)
Postoperative <24 h	1 (0–2)	1 (0–2)
Postoperative >24 h	0 (0–0)	0 (0–0)
Total	3 (2–5)	3 (2–5)

Values are median (interquartile range). There were no significant differences between groups

the early postoperative phase and for the first 24 h after surgery remained significant.

Blood loss can be related to individual surgical ability and technique. One of the three surgeons had significantly greater losses than others; however, exclusion of data from this individual did not change the results of intergroup comparison.

Independent assay of the plasma levels of aprotinin achieved dictated a protocol change to reach levels similar to those observed in cardiac studies. The maintenance infusion dose was therefore doubled from $0·5 \times 10^6$ KI units/ml/h (standard dose) to 1×10^6 KI units/ml/h (high dose) to achieve this. The median intraoperative aprotinin plasma level was 93 (range 51–222) KI units/ml for those treated with the standard regimen and 146 (range 95–334) KI units/ml for those who received the higher infusion dose ($z = 4·15$, $P < 0·001$). Patients treated with the initial standard aprotinin infusion or the higher dose were compared separately with controls; the results were similar to those seen with the whole cohort of patients but there was a dose-related effect for blood loss on to swabs and for the early postoperative period (*Fig. 1*). No correlation was found between mean intraoperative aprotinin level and any of the blood loss or transfusion parameters.

Table 4 Complications of surgery for aprotinin- and placebo-treated patients

Complication	Aprotinin	Placebo
Death	2	4
Cardiac		
Myocardial infarction	1	3
Arrhythmias	4	2
Left ventricular failure	0	2
Thromboembolic		
Deep vein thrombosis	1	1
Pulmonary embolus	2	1
Infective		
Chest infection	6	4
Non-A non-B hepatitis	1	0
Non-specific diarrhoea	2	1
Urinary tract infection	1	1
Sepsis unspecified	1	1
Other		
Surgical	8	4
Rash	1	2
Stroke	1	0
Urinary outflow obstruction	1	0
Renal failure	0	1

Four patients died before the trial protocol was complete. Two further patients died within 30 days of operation, one from left ventricular and renal failure, the other from a chest infection and possible pulmonary embolus; the 30-day mortality rate was 4·5 per cent. Other complications were similar (*Table 4*).

Discussion

This study confirms the safety of aprotinin for use in heparinized patients undergoing cardiovascular surgery. The mortality and morbidity rates are consistent with those in other published series[11,12] and no excess of complications occurred in patients treated with aprotinin compared with the placebo group. In particular, there were no excess thrombotic events such as myocardial infarction or pulmonary embolus (*Table 4*).

Aprotinin certainly affects surgical haemostasis, but not to the degree seen in cardiopulmonary bypass studies[4–7]. The drug significantly reduces intraoperative blood loss collected on to swabs and wound drainage in the first 24 h following surgery. Unfortunately a reduction in overall transfusion requirement has not been demonstrated, nor was overall blood loss significantly reduced by aprotinin.

During surgery blood loss occurs either as oozing which is collected on to swabs or as vessel bleeding, which is usually removed using a sucker. In aortic surgery much of the blood loss falls into the latter category, when the aorta is opened and at the time of testing anastomoses. When technical problems develop during surgery which lead to excessive blood loss, such as a leaking anastomosis or when vessels are deliberately flushed to eliminate debris, aprotinin cannot be expected to reduce blood loss and transfusion requirement. However, the elimination of patients with excessive 'surgical' bleeding by subgroup analysis did not affect the outcome; these patients were evenly distributed between the groups.

In the second phase of the study, an increased dose produced a significant rise in plasma aprotinin level. No significant correlation between any of the blood loss or transfusion parameters and blood plasma levels was shown; however, comparison of the two groups of aprotinin-treated patients with controls demonstrated a dose-related response. Plasma aprotinin levels observed in this study, even after modification of the protocol, did not reach those seen in cardiac studies. This may reflect the pump loading dose of an additional 2×10^6 KI units used for cardiac patients. It is unlikely that, even with higher plasma levels of aprotinin, the results of the study would have been materially different as the blood loss data were similar for treated and control groups with the high-dose regimen. In cardiac surgery the membrane oxygenator has a large foreign surface over which blood must pass, whereas the prosthetic surface in patients having aortic reconstruction is small. The precise mechanism of action of aprotinin is uncertain, but it does stabilize platelet membrane glycoproteins as well as exerting a powerful antifibrinolytic action. Platelet activation and hyperfibrinolysis certainly occur during cardiac surgery and, although they are also seen during elective aortic surgery, the effect is less prominent[13,14]. Cardiac surgeons presently reserve aprotinin for repeat operations or patients with sepsis because blood loss during primary aortocoronary grafting has been reduced by technical advances. Patients who undergo aortic reconstruction may subsequently need cardiac surgery. Prior treatment with aprotinin precludes its use because of the risk of a hypersensitivity reaction.

Aprotinin clearly has a role in operations involving excessive activation of platelets and the fibrinolytic system, in those involving large raw surfaces or in patients with bleeding caused by aspirin. Suprarenal aortic aneurysm grafting and surgery of ruptured aneurysms involve these processes and further studies are required in these situations. However, the small reduction in blood loss in patients treated with aprotinin does not justify its use in routine elective aortic reconstruction.

Acknowledgements

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Surgical workshop

Technique for rapid control of bleeding from an aortoenteric fistula

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Aortoenteric fistula secondary to graft infection has a high mortality rate[1]. The management of such fistulas has been the subject of debate, largely because of the operative risks associated with repair[2]. A technique of endovascular balloon occlusion is described for arresting haemorrhage in a patient exsanguinating from an aortoenteric fistula which provides time for resuscitation and operative repair.

Surgical technique

The femoral artery or limb of a bifurcated aortic graft is exposed through a standard groin incision. Arteriography is performed to confirm the presence of a fistula (*Fig. 1a*). A 30-mm angioplasty balloon (Optiplast-Gambro, Sidcup, Kent, UK) is passed into the lumen of the graft under fluoroscopic control and positioned at the site of the fistula, which has previously been marked. The balloon is inflated to occlude the fistula (*Fig. 1b*). Once the balloon is in position, definitive repair of the fistula can be accomplished by excision of the infected graft, *in situ* replacement with a rifampicin-bonded prosthesis and closure of the duodenal defect.

This technique has been used in two patients who presented with hypovolaemic shock due to upper gastrointestinal haemorrhage. One patient made a good recovery and was discharged home. The other died from multiorgan failure in the intensive care unit after operation.

Discussion

Balloon tamponade has been used to arrest haemorrhage from sites such as the oesophagus and bladder. Transluminally placed endovascular grafts have been used successfully to control bleeding in patients with arterial trauma[3].

This technique for patients with haemorrhage from an aortoenteric fistula is quick and gains valuable time for stabilization before definitive surgery. The difficulty of repeat aortic surgery means that early control is particularly valuable.

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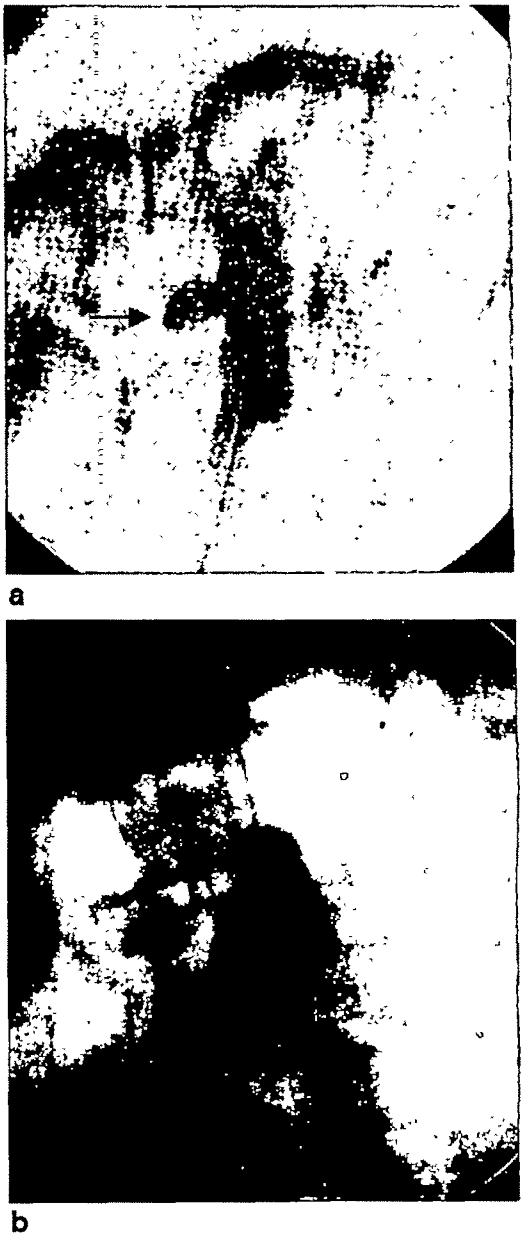

Fig. 1 a Confirmation of the diagnosis of aortoenteric fistula (arrow) by angiography. b Occlusion of the fistula by inflation of the angioplasty balloon

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Colour duplex scanning and pulse-generated run-off for assessment of popliteal and cruropedal arteries before peripheral bypass surgery

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Background This prospective pilot study compared the diagnostic accuracy of duplex scanning and pulse-generated run-off (PGR) with intra-arterial digital subtraction angiography (IADSA) for assessment of popliteal, crural and pedal arteries, and explored the reliability of investigation with the combination of duplex scanning and PGR in patients who needed femorodistal reconstruction.

Methods In 23 limbs, 345 arterial segments were graded independently with duplex scanning and IADSA as normal, stenosed or occluded and compared using weighted κ analysis. PGR was rated as good, poor or no run-off and compared with pedal arch patency on IADSA. Based on information derived from duplex scanning and PGR a vascular surgeon proposed treatment and the distal anastomosis site for bypass, which was compared with definitive treatment as determined by IADSA.

Results Overall agreement between duplex scanning and IADSA for popliteal and crural arteries was moderate (κ 0·47, 95 per cent confidence interval (c.i.) 0·39–0·55) with best agreement within the popliteal and proximal tibial arteries. Agreement within pedal arteries was fair (κ 0·35, 95 per cent c.i. 0·17–0·53). PGR detected good run-off in five of 21 pedal arteries shown to be occluded on IADSA. In 16 of 23 patients treatment based on duplex scanning and PGR was identical to that based on IADSA. Eight of eleven femoropopliteal bypasses were predicted accurately.

Conclusion Operative strategy could have been based on investigation by duplex scanning and PGR in a substantial number of patients scheduled for femoropopliteal bypass surgery. Agreement between duplex scanning and IADSA within very distal arterial segments was fair.

Duplex scanning has the potential to acquire a central place in the investigation of patients with arterial occlusive disease of the leg. A recent meta-analysis demonstrated that duplex scanning is an accurate diagnostic tool and may guide endovascular and surgical interventions in patients with symptomatic atherosclerotic lesions in the aortoiliac and femoropopliteal arteries[1]. Few studies have evaluated duplex scanning for assessment of the infrageniculate arteries[2–4]. Because no unequivocal criteria for detection of haemodynamically significant lesions are available and the number of patients studied remains limited, diagnostic accuracy of duplex scanning is too low for reliable clinical decision making in patients who need a femorodistal reconstruction. Therefore, angiography is still a prerequisite for assessment of outflow vessel quality and determination of distal anastomosis site. The distal run-off can be visualized adequately by intra-arterial digital subtraction angiography (IADSA), but is sometimes difficult because of low flow or movement artefacts.

Pulse-generated run-off (PGR) is a non-invasive technique that gives a semiquantitative analysis of each of the crural arteries and their relative contribution to the pedal arch. PGR correlates well with peripheral vascular resistance and may be a more physiological measure of distal run-off[5,6]. Additionally, PGR has been shown to detect more patent vessels than angiography[5,7].

In this prospective study the diagnostic accuracy of duplex scanning and PGR was compared with that of IADSA for assessment of the run-off arteries in patients awaiting femorodistal bypass grafting. The potential for a completely non-invasive investigation with the combination of duplex scanning and PGR was explored.

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Patients and methods

Between August 1994 and February 1995, 23 non-consecutive patients admitted for incapacitating claudication ($n = 2$), ischaemic rest pain ($n = 12$) or tissue loss ($n = 9$) were studied. Twenty-three legs were examined with colour duplex imaging, PGR and biplanar IADSA Median age of the patients was 71 (range 29–85) years; nine patients were men, seven were diabetic and 13 were smokers. Prior duplex scanning of the aortoiliac and femoropopliteal arteries revealed no lesions suitable for percutaneous transluminal angioplasty (PTA).

Colour duplex imaging was performed by a vascular technician (J v.G.) with a Hewlett Packard Sonos 1000 (Andover, Massachusetts, USA) scanner with a 4·5- and 7·5-MHz imaging transducer and 3·7- and 5·5-MHz Doppler probes respectively. For practical reasons, examination started at the ankle with the patient supine. The anterior and posterior tibial arteries were identified by detection of a colour signal or the presence of the arterial wall in case of occlusion. To avoid mistaking the posterior tibial artery for the peroneal artery, imaging started in the posterior tibial artery which was followed from the ankle to its origin at the tibioperoneal trunk. When identification was difficult, compression of the accompanying veins was used as a road map. Distally, the posterior tibial artery was followed to the common plantar artery into the pedal arch. The lateral and medial plantar arteries were not examined. Distally, the anterior tibial artery was followed via the dorsal pedal artery into the deep plantar artery and proximally back to its origin from the popliteal artery. Then the patient turned prone for examination of the popliteal artery, tibioperoneal trunk, peroneal artery and the origins of the anterior and posterior tibial arteries.

Patency of the suprageniculate and infrageniculate arteries, tibioperoneal trunk, proximal, middle and distal third of the three crural arteries and, at the level of the foot, the dorsalis pedis, common plantar and deep plantar arteries (a total of 15 segments) was graded as follows: 2 for no or minor vessel wall irregularities as seen on B-mode imaging and patent lumen assessed by presence of a colour signal; 1 for severe vessel wall irregularities (B mode), diffuse luminal narrowing (colour Doppler) or an isolated subtotal stenosis; and 0 for occlusion as determined by the absence of colour flow and Doppler signal

PGR was performed by an independent investigator (A.E.P.) with the patient supine. A cuff was placed around the upper calf and inflated 50 times per min to a pressure of 300 mmHg. Thus, a pulsatile flow was generated and recorded with an 8-MHz continuous-wave pencil Doppler probe at the dorsalis pedis, common plantar and peroneal arteries. Each vessel scored 2 for a biphasic signal, 1 for a monophasic signal and 0 for an absent signal. PGR signals were interpreted as good run-off (biphasic signal), poor run-off (monophasic signal) or no run-off (no signal).

Biplanar selective IADSA was performed in all patients on the day after non-invasive evaluation, using an antegrade puncture technique. Non-ionic contrast (Iohexol (Nycomed, Oslo, Norway) 350 mg iodium/ml) was administered by constant mechanical injection with a volume of 10 ml in 2 s with the catheter tip in the proximal or distal superficial femoral artery (SFA). Anteroposterior and lateral views were obtained in all patients and evaluated by a radiologist (J.A.R.), blinded to the non-invasive results. Popliteal, crural and dorsal pedal artery patency was graded as 2 for minor vessel wall or no irregularity, 1 for severe irregularity, diffuse luminal narrowing or isolated subtotal stenosis, and 0 for occlusion. The common and deep plantar artery scored 2 for direct filling of the pedal arch, 1 for indirect filling of the pedal arch and 0 for no filling of the pedal arch.

A vascular surgeon (D.A.L.), who was unaware of the angiographic findings, determined therapeutic management based on the non-invasive information (i.e. PTA, surgical revascularization or no options for reconstruction) or considered non-invasive evaluation to be non-diagnostic and IADSA required. Definitive treatment was instigated by the staff vascular surgeons, who were blinded to the results of duplex scanning and PGR, based on the angiographic information.

Interobserver variation of IADSA readings was calculated according to the method of Fleiss[8] for agreement for multiple observers and multiple test results. Agreement between duplex scanning and IADSA (scored by the radiologist) on patency of the respective vascular segments was compared in weighted κ analysis[9]. κ expresses the probability of agreement beyond chance. Strength of agreement can be interpreted as poor (κ less than 0·20), fair (κ 0·21–0·40), moderate (κ 0·41–0·60), good (κ 0·61–0·80) or excellent (κ 0·81–1·00). Sensitivity and specificity of duplex scanning compared with IADSA as 'gold standard' were calculated for detection of an occlusion in the respective vascular segments. The proposed therapeutic management and distal anastomosis site based on information acquired non-invasively were compared with definitive therapy.

Results

Interobserver variation of intra-arterial digital subtraction angiography readings

All angiograms were scored by three observers (D.A.L., J.A.R., M.J.H.M.J.) with good overall agreement on patency: D.A.L. *versus* M.J.H.M.J. κ 0·76 (95 per cent confidence interval (c.i.) 0·69–0·84), D.A.L. *versus* J.A.R. 0·73 (0·65–0·82) and J.A.R. *versus* M.J.H.M.J. 0·64 (0·54–0·73). Interobserver agreement was moderate within the popliteal artery (κ 0·46, 95 per cent c.i. 0·33–0·60), good within anterior (κ 0·59, 95 per cent c.i. 0·48–0·71) and posterior (κ 0·67, 95 per cent c.i. 0·56–0·79) tibial arteries, but decreased significantly within the peroneal artery (κ 0·42, 95 per cent c.i. 0·30–0·53) and pedal arteries (κ 0·33, 95 per cent c.i. 0·21–0·46).

Duplex imaging of popliteal and crural arteries

Of 276 popliteal and crural artery segments two (0·7 per cent) could not be imaged adequately with duplex imaging, whereas in 17 (6·2 per cent) IADSA was non-diagnostic. This left 259 segments for comparison with moderate agreement (overall κ 0·47, 95 per cent c.i. 0·39–0·55). Raw data in *Table 1* show that, in general, duplex imaging gave a more optimistic assessment of patency than IADSA. There was moderate agreement on patency of the popliteal, anterior and posterior tibial arteries and poor agreement within the peroneal artery and tibioperoneal trunk (*Table 2*). Sensitivity for detection of an occlusion was moderate for the popliteal arteries and tibioperoneal trunk with a high specificity. In the proximal and middle segment of the anterior and posterior tibial arteries diagnostic accuracy was high, but this declined in the distal segments. Accuracy for assessment of the peroneal artery was poor.

Duplex imaging of pedal arteries

Duplex scanning and IADSA were both non-diagnostic in eight of 69 pedal artery segments. The deep plantar artery in particular was difficult to visualize, with both duplex scanning ($n = 5$) and IADSA ($n = 3$). This left 54 segments for comparison with fair overall agreement (κ 0·35, 95 per cent c.i. 0·17–0·53). Best agreement was found within the common plantar artery, whereas agreement was poor within the dorsalis pedis artery (*Table 2*). This is also reflected in the respective sensitivities and specificities of duplex scanning for detection of an occluded pedal artery.

Pulse-generated run-off

In 21 of 23 patients the dorsalis pedis artery could be assessed adequately with IADSA and in two of these PGR was non-diagnostic, leaving 19 patients for comparison. In three of eight patients with an occluded dorsalis pedis artery on IADSA a biphasic signal was obtained with PGR. In all 11 patients with a patent dorsalis pedis artery a monophasic or biphasic signal was also recorded. In two of 13 angiographically occluded common plantar arteries

Table 1 Crural vessel patency assessed with duplex scanning and intra-arterial digital subtraction angiography as gold standard in 276 segments

	Intra-arterial digital subtraction angiography				
Duplex scanning	Normal	Severe disease	Occluded	Non-diagnostic	Total
Normal	48	38	14	1	101
Severe disease	18	17	19	5	59
Occluded	5	16	84	9	114
Non-diagnostic	0	0	0	2	2
Total	71	71	117	17	276

Overall κ 0·47 (95 per cent confidence interval 0·39–0·55)

Table 2 Agreement between duplex scanning and intra-arterial digital subtraction angiography on vascular patency and diagnostic accuracy of duplex scanning for detection of an occlusion

Arterial segment	No of segments	κ	Sensitivity	Specificity
Popliteal and crural arteries				
Suprageniculate popliteal	23	0·56 (0·30 to 0·83)	5 of 8	13 of 15
Infrageniculate popliteal	23	0·37 (0·05 to 0·68)	2 of 4	18 of 19
Tibioperoneal trunk	22	0·25 (−0·04 to 0·53)	3 of 6	15 of 16
Proximal anterior tibial	22	0·46 (0·24 to 0·69)	10 of 11	9 of 11
Middle anterior tibial	22	0·75 (0·52 to 0·98)	12 of 14	8 of 8
Distal anterior tibial	21	0·52 (0·25 to 0·79)	6 of 10	10 of 11
Proximal posterior tibial	22	0·48 (0·22 to 0·74)	12 of 15	7 of 7
Middle posterior tibial	21	0·56 (0·30 to 0·83)	13 of 16	5 of 5
Distal posterior tibial	21	0·38 (0·02 to 0·75)	11 of 15	5 of 6
Proximal peroneal	22	0·22 (−0·06 to 0·50)	2 of 4	11 of 18
Middle peroneal	21	0·43 (0·15 to 0·71)	5 of 8	11 of 13
Distal peroneal	19	0·11 (−0·25 to 0·47)	3 of 6	9 of 13
Pedal arteries				
Dorsalis pedis	19	0·21 (−0·11 to 0·54)	2 of 6	11 of 13
Deep plantar	16	0·36 (0·04 to 0·67)	3 of 7	8 of 9
Common plantar	19	0·42 (0·13 to 0·70)	7 of 13	6 of 6

Values in parentheses are 95 per cent confidence intervals

Table 3 Proposed treatment based on the combination of duplex scanning with pulse-generated run-off and definitive treatment as instigated on the basis of intra-arterial digital subtraction angiography

	Proposed treatment (duplex scanning and PGR)	Definitive treatment (IADSA)
No reconstruction	4	4
PTA of superficial femoral artery	1	3
Bypass surgery	14	16
Non-diagnostic	4	0

PGR, pulse-generated run-off; IADSA, intra-arterial digital subtraction angiography, PTA, percutaneous transluminal angioplasty

a biphasic signal was recorded, as well as in all six patent common plantar arteries. Thus, no false-negative results were obtained with PGR for the pedal arch arteries.

Management

In four patients both non-invasive evaluation and IADSA revealed no options for vascular reconstruction and these patients were treated conservatively ($n = 3$) or by primary lower limb amputation ($n = 1$) (*Table 3*). Three patients eventually had PTA of the SFA, one because of poor general condition, one because a 99 per cent stenosis in the adductor canal was mistaken for an occlusion by duplex scanning, and in the third the presence of two significant stenoses in the SFA were not recognized by duplex scanning. Sixteen patients underwent vascular reconstruction. Eight of 11 infrageniculate popliteal artery bypasses and three of five crural artery bypasses were predicted correctly based on the non-invasive investigation. In four patients non-invasive evaluation yielded insufficient information to plan definitive treatment and IADSA was considered necessary. Three of these patients required a bypass, one each to the infrageniculate popliteal, anterior and posterior tibial artery, and one patient was treated with PTA of the SFA. In summary, in 16 of 23 patients treatment, including distal anastomosis site, was predicted accurately by the non-invasive investigation with duplex scanning and PGR.

Discussion

In the present study there was moderate agreement between duplex scanning and IADSA for assessment of suprageniculate popliteal, posterior and anterior tibial and common plantar artery patency. Agreement was poor to fair for the other arterial segments.

The results for the crural arteries are in accordance with previous work Caster *et al.*[3] could visualize significantly fewer peroneal than anterior and posterior tibial artery segments, resulting in lower accuracy for detection of occlusions. This can be explained by the limitations of anatomy and operator experience. The depth of the artery from the skin surface and the fascial borders between transducer and the artery can obstruct adequate visualization. Poor accuracy may also be explained by the difficult angiographic assessment of the peroneal artery, which in this study showed significantly lower interobserver agreement than the tibial arteries.

To date, no published data have compared duplex scanning and IADSA for assessment of the pedal arteries. The relatively large number of non-visualized pedal artery segments, both with duplex scanning and IADSA, reflects the limitations of both techniques. Agreement between duplex scanning and IADSA was disappointing, with moderate agreement for the common plantar artery as the best result. So far, it is uncertain whether poor agreement is caused by shortcomings of IADSA or duplex scanning.

Although IADSA is the best available accepted technology at this time, it has its limitations. First, little is known about interobserver variability of interpretation of arteriograms, especially of crural and pedal arteries. Bruins Slot *et al.*[10] found poor interobserver agreement for translumbar aortography of the entire lower vascular tree (κ range 0·068–0·328) with exception of the SFA (κ

0·513). Jager *et al.*[11] found good agreement (κ 0·63) between two radiologists for assessment of arteriograms from the aorta to the popliteal artery. Leng *et al.*[12] found high intraclass correlation coefficients indicating good interobserver correlation for determination of SFA stenosis, but individual measurements varied by as much as 30 per cent. In the present study agreement was good for the tibial arteries, moderate for the popliteal and peroneal arteries and poor for the pedal arteries. Despite the use of digital subtraction techniques, angiography sometimes fails to identify vessels that are patent on intraoperative angiography[13,14], dependent Doppler examination[15] or magnetic resonance angiography[16]. This could further explain the poor agreement of duplex scanning with IADSA within the pedal arteries, where sensitive duplex scanning detects flow in arteries not visualized with IADSA. A pitfall of duplex scanning, however, was the detection of signals in what appeared to be collaterals on angiography, especially in the dorsalis pedis artery.

The discrepancy between angiography and PGR for run-off detection has been noted before[5,6]. Despite a high correlation between IADSA and peripheral resistance, IADSA was inferior to PGR in single calf vessels. In the present study PGR also detected more patent pedal arteries than IADSA. In a series of 100 vein bypasses, Scott *et al*[17] found 1-year secondary patency rates for grafts to a complete, incomplete and occluded pedal arch determined by PGR of 88, 75 and 9 per cent respectively. Graft failure within 1 month occurred significantly more often in reconstructions to a single calf vessel than to the popliteal artery, when the pedal arch was incomplete or occluded. Davies *et al.*[18] reported 78, 90 and 38 per cent 1-year patency rates, with respect to complete, incomplete and occluded pedal arch assessed with PGR.

Despite the limited agreement on crural and pedal artery patency, therapeutic management was accurately predicted based on duplex scanning and PGR information in 16 of the 23 patients in this study. Decisions for femoropopliteal bypass grafting could have been made reliably. However, decision making in vascular surgery is subject to significant variability, caused by diversity in surgeons' clinical approach to individual situations[19]. The assumption that a single vascular surgeon represents the clinical approach of an entire group may not be right. The present results justify further investigation of the role of duplex scanning combined with PGR in clinical decision making with respect to distal bypass surgery. Indeed 16 of 23 may be an underestimate, given the limitations of IADSA and the possibility of duplex scanning and PGR detecting more run-off vessels and improving patients' outcome.

Duplex scanning is a reliable investigation of the aortoiliac and femoropopliteal arteries and may guide intervention within these segments[1,20]. The results of this study indicate that, in patients who require peripheral bypass surgery, duplex scanning can assess crural artery patency accurately. The discrepancy between duplex scanning and IADSA within the pedal arteries was substantial and it remains unclear whether this is due to shortcomings of duplex scanning or IADSA. Despite the small number of patients and the retrospective determination of accuracy of proposed treatment strategy, this study shows that a substantial reduction in diagnostic angiography before femoropopliteal bypass may be possible. Further study is needed to define the role of duplex scanning and PGR for complete non-invasive investigation in patients who need a femorodistal reconstruction.

Acknowledgements

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Case report

Magnetic resonance imaging in the evaluation of a high-velocity gunshot wound to the thigh

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Plain radiographs in the investigation of ballistic trauma allow the identification of bony injury and metallic fragments[1]. Despite the ferromagnetic properties of some ballistic materials, magnetic resonance imaging (MRI) is generally safe provided it is not used in those with fragments near to neural and vascular structures[2,3]. The exact role of MRI remains to be defined[4]. A patient with a high-velocity gunshot wound to the thigh in which MRI identified soft tissue damage, more extensive than was clinically apparent, is reported.

Case report

A 22-year-old soldier was shot at a range of 20 m receiving an entry and exit wound in the left buttock and lower left thigh respectively. There was no clinical evidence of neurovascular injury. Plain radiographs excluded a fracture and retained metallic fragments. Arteriography was not performed. Wound debridement and fasciotomies were carried out at 9 h. In the UK, at 8 days, MRI showed swelling of the thigh with evidence of further necrotic muscle on the medial side of the anterior compartment remote from the bullet tract and previous surgery. A signal void suggestive of a false aneurysm was identified (*Fig. 1*).

At operation, thigh compartment pressures were normal. The wound on the lateral aspect of the thigh measured 50 cm × 15 cm and was healthy. The common femoral artery was exposed and an incision extended distally to the adductor canal Further necrotic muscle, as predicted by MRI, was debrided and a false aneurysm of the distal profunda femoris artery was ligated. The two wounds were closed by delayed primary suture and split skin grafts at 2 weeks.

Discussion

This patient demonstrates the value of MRI in the investigation of ballistic trauma. It identified clinically unsuspected muscle damage and a significant vascular injury. Without this information no attempt would have been made to explore beyond the already wide and adequate debridement performed at the initial surgery. Rupture of the false aneurysm or infection of the necrotic muscle would certainly have compromised the patient's recovery.

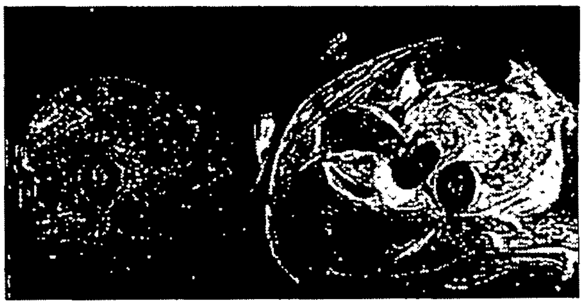

Fig. 1 Magnetic resonance imaging of the left thigh. An axial short tau inversion recovery (STIR) sequence (TE (time to echo) 30, TR (time to repeat) 2258, TI (inversion time) 100; 0·5-Tesla Picker Asset) through the mid thigh demonstrates extensive tissue damage with profunda aneurysm

The ability of MRI to demonstrate soft tissue damage is unique, ensuring an increasingly important role in the investigation of trauma[5]. Faster scan times, magnetic resonance angiography, open magnetic design, and the future potential to identify tissue hypoxia will expand this role further. MRI should be considered early in the investigation of both blunt and penetrating trauma to the extremities. Its role in the military environment is being explored.

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Ultrasonographic imaging of mycetoma

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Introduction The ultrasonographic appearance of mycetoma is described in this prospective study.

Methods One hundred patients with foot swellings had sonographic evaluation of the swelling and surgical excision within 2 weeks of ultrasonography. The histopathological findings were compared with the preoperative images. Some of the excised swellings and grains were also imaged and compared with the *in vivo* findings.

Results The mycetoma grains, their capsules and the accompanying inflammatory granulomas have characteristic ultrasonographic appearances. In eumycetoma lesions, the grains produce numerous, sharp hyper-reflective echoes and there are single or multiple thick-walled cavities with no acoustic enhancement. In actinomycetoma, the findings are similar but the hyper-reflective echoes are fine, closely aggregated and commonly settle at the bottom of the cavities. None of the non-mycetoma foot swellings (which included lipoma, ganglion, foreign body granuloma and others) studied had these features.

Conclusion Ultrasonography is simple, non-invasive, quick, reproducible and acceptable to patients. Mycetoma has characteristic ultrasonographic features. Furthermore, ultrasonography delineates the extent of mycetoma more accurately than clinical examination alone.

Mycetoma is a chronic granulomatous subcutaneous infection caused by true fungi (eumycetoma) or by higher bacteria of the class actinomycetes (actinomycetoma). The disease is endemic in tropical and subtropical areas[1,2]. Mycetoma has a prolonged, progressive and indolent course and, if untreated, ultimately leads to destruction of deeper tissues and bone resulting in deformity and disability which may necessitate amputation[3].

The triad of a painless subcutaneous mass, draining sinuses and grains (if present) is characteristic of mycetoma. The diagnosis may be difficult in early lesions especially before the appearance of sinuses and grains. The differential diagnosis includes a variety of soft tissue tumours and granulomas[4].

Successful surgical excision is dependent on accurate diagnosis and determination of the extent of the lesion which is often difficult before operation[1,2]. A non-invasive method to help in the preoperative diagnosis of mycetoma would be useful particularly for lesions not associated with discharging sinuses. This report evaluates the use of ultrasonographic imaging in the management of mycetoma.

Patients and methods

This was a prospective study of 100 patients who had sonographic evaluation of foot swellings by a radiologist unaware of the clinical findings. The swellings were imaged in different planes with a Toshiba Sol, EUB-25 M, real-time ultrasound linear scanner with a 3·75-MHz transducer. The transducer was covered with a cellophane bag to avoid damage from the rough skin or contamination. The images were printed on Polaroid films and the findings were recorded in a check list (*Table 1*) which included the sonographic features of the common subcutaneous swellings. All patients had the swellings excised within 2 weeks of the ultrasonographic examination and the histopathological findings were compared with the preoperative ultrasonographic images.

In addition, some of the surgically excised lesions and grains were imaged. The excised lesions were placed on plates and the grains were placed in water-filled plastic bags. The ultrasonographic findings were compared with preoperative results.

Results

The 100 patients with foot swellings included 75 men and 25 women with a mean(s.d.) age of 28(12) years. The mean(s.d.) duration of the swellings was 5(1) years. Thirty-seven patients had discharging sinuses.

The sonographic and histopathological findings of the surgically removed swellings are shown in *Tables 1* and *2*.

In all eumycetoma swellings, there were numerous isolated sharp hyper-reflective echoes corresponding to the grains in the lesion. Single or multiple thick-walled

Table 1 Ultrasonographic features of the examined swellings

Finding	Mycetoma	Non-mycetoma
Cavities		
Single	10	10
Multiple	47	0
Thick wall	57	5
Thin wall	0	5
Debris and filaments	10	3
Acoustic enhancement	0	40
Hyper-reflective echoes		
Fine	22	0
Sharp	35	0
Numerous	50	0
Few	17	0
Isolated	30	0
Aggregated	17	0
Diffuse	10	0
Settled at the bottom of the cavities	22	0
Mass		
Homogeneous	0	20
Echogenic	0	19
Anechoic	0	4

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Table 2 Histopathological diagnosis of the surgically excised swellings

Diagnosis	No.
Eumycetoma	35
Madurella mycetomatis	34
Allescheria boydii	1
Actinomycetoma	22
Streptomyces somaliensis	13
Actinomadura madurae	7
Actinomadura pelletieri	2
Lipoma	11
Ganglion	10
Foreign body granuloma	10
Neuroma	5
Kaposi's sarcoma	3
Fibrosarcoma	2
Haematoma	2

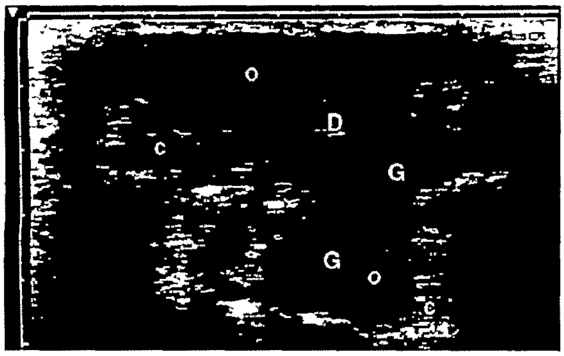

Fig. 1 Transverse scan of a eumycetoma lesion. Note the presence of numerous sharp hyper-reflective echoes which are inconsistent with the eumycetoma grains (G) within the multiple cavities (O). The cavities have thick walls (C) with no acoustic enhancement and contain debris (D)

cavities with no acoustic enhancement were identified in all lesions. In ten swellings, these cavities contained debris and filaments (*Fig. 1*). In actinomycetoma, the findings were similar but the hyper-reflective echoes were fine, closely aggregated and were commonly settled at the bottom of the cavities (*Fig. 2*). These features were not demonstrated in any of the non-mycetoma swellings. The ultrasonographic appearances of non-mycetoma swellings were similar to those reported elsewhere[5,6].

Identification of the hyper-reflective echoes within the lesions was less clear when active sinuses were present. The *in vitro* ultrasonographic features of the excised mycetoma and non-mycetoma lesions were reproducible and identical to the *in vivo* appearances; however, the ultrasonographic features of the grains (hyper-reflective echoes) were clearer on the *in vitro* ultrasonograms.

Discussion

The available diagnostic tests for mycetoma are few and not without limitations. Staining and culture of pus, discharge or biopsy material are the standard methods. Staining grains allows the identification of the causative organisms but is of limited value in differentiating from true fungi[7]. Culture is always necessary for definitive diagnosis. However, the technique is time consuming, chance contamination is common and deep surgical biopsy is always needed. It requires experience and it is not always practical and cost-effective in endemic areas[7]. Serodiagnosis is vitiated by cross-reactivity between actinomycetes and the antigens lack specificity[8,9]. Recently, aspiration cytology of mycetoma was described but when there are no grains in the aspirate the test is of little value[10]. Histopathological examination is useful but carries a substantial risk of spreading mycetoma as deep surgical biopsy is always required[11].

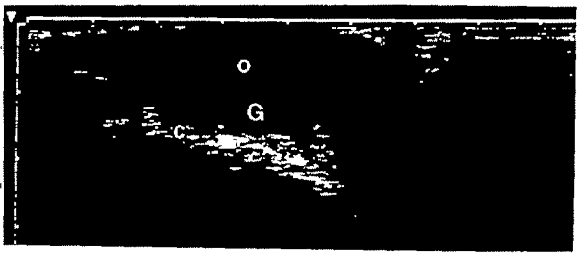

Fig. 2 Transverse scan of an actinomycetoma lesion. Note the haziness of the hyper-reflective echoes (G) and their close aggregation compared with that of eumycetoma grains

It is clear from this study that the differentiation between mycetoma and non-mycetoma lesions can be achieved by the characteristic ultrasonographic appearance (*Table 1*).

Eumycetoma lesions can be differentiated from actinomycetoma by the presence of the sharp bright hyper-reflective echoes which are consistent with black grains. The grain cement substance is probably the origin of these sharp echoes. The grains of actinomycetoma are less distinct. This observation is explained by the consistency, smaller size, individual embedding of the grains and the absence of cement substance in some types of actinomycetoma. The *in vitro* ultrasonographic features of mycetoma lesions were reproducible and identical to the *in vivo* appearances.

The ultrasonographic diagnosis of mycetoma lesions without sinuses was more precise than that of those with sinuses. This is attributed to lack of intimate contact of the transducer with the lesion. The presence of fibrous tissue along the sinus tract could disturb the ultrasonic beam.

The ultrasonographic technique is especially useful in centres where mycological and serological tests are not available and can determine accurately the size and extent of the lesions before surgery.

Real-time ultrasonography can help in the clinical management of patients with mycetoma. It is a simple, rapid, sensitive and non-invasive preoperative diagnostic method which provides information that is difficult to obtain on clinical and radiological examination alone. Although ultrasonography was found to be accurate in identifying the cause of mycetoma it should not be relied upon solely for treating patients until further experience with the technique is gained.

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Outcome and predictors of success of biofeedback for constipation

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Background A study was undertaken to determine outcome and to identify predictors of success for biofeedback for constipation.

Methods Patients who had at least one biofeedback session were evaluated whether or not they completed a treatment course. Parameters assessed included use of cathartics, number of spontaneous bowel movements per week, presence of rectal pain, number of biofeedback sessions and results of anorectal physiology.

Results A total of 194 patients (59 male, 135 female) of median age 71 (range 11–96) years, including 30 with concomitant rectal pain, were treated. The median number of spontaneous bowel movements per week before treatment was 0. Some 35 per cent of patients had complete success (three or more spontaneous bowel movements per week with discontinuation of cathartics), 13 per cent had partial success (fewer than three spontaneous bowel movements per week with continued use of cathartics) and 51 per cent had no improvement. Neither patient age, sex nor duration of symptoms significantly affected outcome. Only 18 per cent of patients who had between two and four sessions had complete success, compared with 44 per cent of those who had five or more ($P < 0.001$). A total of 63 per cent of patients who completed the treatment protocol experienced complete success, compared with 25 per cent of those who self-discharged ($P < 0.0001$).

Conclusions This large study indicates that the success rate of biofeedback for patients with constipation is less than previously reported. However, the success rate improves significantly after five or more sessions and is significantly related to the patient's willingness to complete treatment.

Constipation is a common complaint in Western societies and may be used to depict several different symptoms[1]. Patients who seek medical attention may describe the passage of small dry stools, straining at stool or decreased stool frequency; the latter is the most subjective of these complaints. Epidemiological studies suggest that 95–99 per cent[2,3] of the population of the USA and UK pass at least three stools per week and therefore individuals whose bowel frequency is less than this may be considered constipated[1]. Using this definition, Everhart *et al.*[4] have suggested that 3 per cent of men and 9 per cent of women in the USA are constipated[4].

After organic causes have been excluded, functional disorders of the pelvic floor account for 75 per cent of cases of chronic constipation. For normal evacuation to take place there must be adequate relaxation of the puborectalis muscle, allowing straightening of the anorectal angle and passage of the faecal bolus. Subsequent relaxation of the external anal sphincter muscles makes evacuation possible. Failure of relaxation may result in obstructed defaecation. This condition has been ascribed many synonyms including spastic pelvic floor syndrome[5], anismus[6], non-relaxing puborectalis syndrome[7] and paradoxical puborectalis contraction[8]. Various surgical[9–13] and medical[14] treatments have been tried with partial success but considerable morbidity.

Biofeedback is a process of training individuals to be more aware of, and responsive to, biological information. It can be useful for obstructed defaecation[15–29] and has been used in this institution for several years. The aim of this study was to review a 6-year experience with biofeedback and to identify factors that may predict a successful outcome.

Patients and methods

The medical records of all patients who attended at least one session of electromyography (EMG)-based biofeedback therapy for constipation between February 1989 and August 1995 were reviewed retrospectively. All patients had been referred by either a staff colorectal surgeon or a gastroenterologist and all had had organic disease excluded by physical examination and either barium enema or colonoscopy, as clinically indicated. In addition, anorectal physiological investigation included pan-colonic transit study, anorectal manometry with elicitation of the rectoanal inhibitory reflex, cinedefaecography, pudendal nerve terminal latency assessment and external anal sphincter EMG. These tests were performed as described previously[30–32]. No ambulatory studies were done.

Paradoxical puborectalis contraction was defined as the presence of at least two of the following abnormalities: retention of at least 20 per cent of the colonic markers in the rectum on the fifth day of a transit study, inability to achieve prompt and complete evacuation of barium paste during cinedefaecography with lack of a measurable increase in the anorectal angle between rest and attempted evacuation, or a paradoxical increase in puborectalis muscular activity during needle EMG[25].

Biofeedback training was performed in sessions lasting 1 h supervised by a certified biofeedback therapist Biofeedback was performed with a 12-mm diameter, 45-mm long PerryMeter anal EMG sensor EPS-21 (PerryMeter Systems, Strafford, Pennsylvania, USA) connected to an Orion 8600 (Self Regulation Systems, Redmond, Washington, USA) biofeedback computer.

Training patients to sense the activity of their pelvic muscles began with a detailed explanation of their anatomy and

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physiology. EMG-based biofeedback was then used to enable discrimination between three events – rest, squeeze and push – so that patients learned or relearned proper coordination of the pelvic muscles. After insertion of the anal sensor, patients redressed and sessions were conducted with patients seated on a standard chair. Patients were taught squeeze–relax (Kegel) exercises and were encouraged to practise these manoeuvres at home. The push exercise is not done at home in the same manner as the Kegel exercises but is practised only during biofeedback sessions. Along with EMG-based biofeedback, additional advice on the adoption of proper posture during evacuation and on reducing dependence on laxatives, suppositories, enemas and digitation was presented during these sessions. In addition, the therapist attempted to shift patients' focus away from the ubiquitous preoccupation with their bowel habits. Various stress management techniques were used and, in particular, patients were encouraged to take daily physical exercise. Patients were instructed to keep a daily log of their practise exercises, physical exercise, bowel movements, use of cathartics (laxatives, enemas and suppositories) and digitation. All patients were encouraged to increase the amount of insoluble fibre and non-alcoholic decaffeinated fluids in their diet. However, compliance with this instruction was difficult to assess.

The objective assessment of biofeedback therapy was twofold. First the number of assisted and spontaneous bowel movements during the week before commencement of treatment and during the week before the final session were recorded. The use of cathartics and digitation was also noted. Second, the electrical activity of the puborectalis and external anal sphincter muscles was quantified. Values at rest and during maximum squeeze were obtained during every session. Paradoxical puborectalis contraction by intra-anal EMG was defined as a push value of 2·5 mV or more, or a difference between the rest and push values greater than 1·0 mV.

Outcome was divided into three categories. Patients were deemed to have complete success if they passed three or more spontaneous bowel movements per week without the aid of cathartics or digitation. Partial success was defined as the passage of fewer than three spontaneous bowel movements per week with a reduced dependence on assistance. Patients who had no improvement in either of these parameters were graded as failed.

Patients continued biofeedback sessions until they had control of the pelvic floor musculature as demonstrated by EMG, and had a reduction in the use of cathartics and resolution of the constipation as indicated by the diary.

Statistical analysis was by Fisher's exact test, performed using InStat V2.02 software (GraphPad Software, San Diego, California, USA). $P < 0{\cdot}05$ was considered statistically significant.

Results

A total of 194 patients attended at least one session of biofeedback training for constipation, including 30 patients who had concomitant rectal pain. Patients who had biofeedback treatment exclusively for the treatment of rectal pain were excluded. There were 135 female patients with a median age of 71 (range 12–96) years and 59 male patients of median age 67 (range 11–92) years. The median duration of symptoms was 14 years (range from 2 months to lifelong); 49 patients (25 per cent) reported lifelong constipation.

The most common previous medical condition was haemorrhoids (32 patients). Twenty patients had a history of diverticular disease. Nineteen patients reported previous depression or anxiety, including one who had been treated for bulaemia nervosa. Ninety-eight patients had had previous surgery, with gynaecological surgery being the most prevalent (34 patients) followed by abdominal surgery (30), anorectal surgery (27), spinal surgery (nine), prostatic resection (two) and hip replacement (one).

Thirty-one patients (16 per cent) attributed the symptoms to a precipitating event or condition. Nineteen patients cited stress as the major contributory factor, whereas 12 attributed their symptoms to previous surgery (abdominal surgery, five; haemorrhoidectomy, four; spinal surgery, three).

The majority (70 per cent) of patients discharged themselves before their condition had resolved to the therapist's satisfaction. Sixteen patients who attended only one session of biofeedback were excluded from further analysis. Of the remaining 178 patients, 132 (74 per cent) had had no spontaneous bowel movements per week before the commencement of biofeedback therapy. Ninety-four patients (53 per cent) used at least one cathartic per day and only 23 (13 per cent) denied cathartic use; seven of these 23 patients reported the use of digitation to achieve evacuation.

Overall 63 patients (35 per cent) had complete success, 24 (13 per cent) had partial success and 91 (51 per cent) had no improvement. Patients who had complete success had a significant increase in the number of spontaneous bowel movements per week ($P < 0{\cdot}0001$) and a significant decrease in weekly cathartic use ($P < 0{\cdot}0001$) (*Table 1*).

The success of treatment was not significantly related to age (patients aged 65 years or less, 31 per cent *versus* 40 per cent in those aged over 65 years, $P = 0{\cdot}24$), sex (male patients 37 per cent *versus* 33 per cent in female patients, $P = 0{\cdot}64$) or duration of symptoms (*Table 2*). Concomitant rectal pain did not influence outcome as 30 per cent of patients with rectal pain had a completely successful outcome compared with 36 per cent of those with constipation alone ($P = 0{\cdot}55$). The success of treatment was significantly related to the number of sessions attended. Only 18 per cent of patients who attended between two and four sessions experienced complete success, compared with 44 per cent of the 118 who attended more than four sessions ($P < 0{\cdot}001$) (*Table 3*). Patients who self-discharged attended a median of 5

Table 1 Changes in weekly spontaneous bowel movements and cathartic use related to outcome

	Spontaneous bowel movements per week		Cathartic use per week	
	Before	After	Before	After
Complete success	0(0·3)	6(0·6)	7(0·4)	0(0·2)
Partial success	0(0·9)	1(0·7)	4(0·6)	3(0·5)
No success	0(0·4)	0(0·2)	5(0·7)	5(0·6)

Values are median(s.e.)

Table 2 Outcome according to duration of symptoms

Duration of symptoms (years)	No. of patients	Complete success	Partial success	No success
≤2	42	12 (29)	9 (21)	21 (50)
≤5	62	18 (29)	12 (19)	32 (52)
≤10	75	23 (31)	14 (19)	38 (51)
≥10	—	33 (39)	8 (9)	44 (52)

Values in parentheses are percentages

Table 3 Outcome according to number of biofeedback sessions attended

No. of sessions	No. of patients	Complete success	Partial success	No success
2–4	60	11 (18)	5 (8)	44 (73)
5–7	51	25 (49)	9 (18)	17 (33)
8–10	26	10 (38)	3 (12)	13 (50)
>10	41	17 (41)	7 (17)	17 (41)

Values in parentheses are percentages

(range 2–20) sessions, whereas those discharged by the therapist had a median of 11 (range 5–30) sessions. The rate of complete success in the 29 per cent of patients who completed the prescribed course of biofeedback to the satisfaction of the therapist was 63 per cent. Conversely, success was noted in only 25 per cent of the patients who self-discharged before the completion of therapy ($P < 0.0001$). A significant difference in outcome was noted even in the 69 patients (39 per cent) who self-discharged after five sessions ($P < 0.001$) or the 16 (9 per cent) who self-discharged after ten sessions ($P < 0.05$).

Some 151 patients had manometry before biofeedback. There was no relationship between mean resting or squeeze pressure, length of the high pressure zone, sensory threshold or maximum capacity and the outcome of biofeedback. In addition, 151 patients had cinedefaecography; 100 had a degree of fixed or dynamic descent, 32 had a significant anterior or posterior rectocoele and 15 had a significant intussusception. None of these abnormalities influenced the success of treatment.

There was no treatment-related morbidity recorded. Some patients who had an unsatisfactory outcome were referred for further therapy. Nine were referred for injection of *Clostridium botulinum* type A neurotoxin, and two accepted this treatment. Six had further biofeedback, three had a total abdominal colectomy and one had a transverse loop colostomy.

Discussion

Biofeedback has been employed in the treatment of obstructed defaecation with success rates ranging between 8·3 and 100 per cent[15–29,33]. However, the results are difficult to compare as biofeedback protocols vary considerably between institutions. Some authors have used manometry to display sphincter pressures in an attempt to retrain pelvic floor muscles[16–18,24,33]. Other investigators use surface EMG electrodes placed on the external sphincter and buttocks[19] or mounted on an intra-anal sensor[15,20,21,23,25]. Alternative methods have included these modalities in combination with balloon expulsion and rectal sensation training[15–20]. Bleijenberg and Kuijpers[26] demonstrated the superiority of EMG-based biofeedback over manometric biofeedback. The frequency and length of treatment sessions also varies widely. Some units prefer inpatient protocols[15] whereas other use daily[23] or weekly[25] outpatient sessions. Several authors have encouraged home training[20,21].

The treatment of constipation by biofeedback has been viewed with some scepticism as the low success rate in some studies may simply be a placebo effect. Indeed, two small randomized studies have suggested that conventional treatment alone[34], or muscular retraining without biofeedback[35], achieves similar results to biofeedback-enhanced training. By contrast, other studies show significant improvement in patients who receive biofeedback compared with those treated with conventional medical therapy alone[19,27] or total body relaxation techniques[36].

There may be several reasons for the low success rate in this series. First, the definitions of success used in other studies vary widely. Some authors determine success as an overall increase in stool frequency[21,24,26], a decrease in cathartic use[20,25] or a decrease in symptoms such as pain, bloating and straining[21,24,26]. The definition of complete success in this study was chosen to reflect patients who returned to normal with regard to their bowel habit. Using this definition, Dahl *et al.*[20] reported an overall success rate of 50 per cent at 6 months' follow-up, whereas Loening-Baucke[22] reported overall success in only 37 per cent of patients after 12 months' therapy.

Most of the previous reports have been on children or young adults[15–19,22,34]. The patients in this study represent the oldest series in the literature and the low success rate might have been due to cognitive impairment in these patients. The failure of many patients to improve after fewer than five sessions would support this 'slow learning' hypothesis, as others have reported improvement in all patients after two to four sessions[20]. However, stratifying patients by age did not reveal any significant difference in outcome. Some authors have shown that patients who have had symptoms for many years are particularly resistant to treatment[30], but again stratification of patients by duration of symptoms failed to reveal any differences in the rate of success. The present authors have, however, shown in a previous study that many of the constipated patients in their population have increased levels of somatization as determined by the Minnesota Multiphasic Personality Inventory assessment[37], making this a difficult patient group to treat.

The rate of self-discharge in this study was considerably higher than that in any other study in the literature due in part to the transient elderly population in South Florida. This is unfortunate as the most important predictor of success is completion of therapy.

Despite the low success rate demonstrated in this large series, safety makes biofeedback an attractive treatment option as other therapies are associated with considerable morbidity. Martelli *et al.*[9] performed anorectal myectomy in 62 patients with an overall success rate of 66 per cent but an incontinence rate of 16 per cent. Surgical division or partial resection of the puborectalis is reported to be successful in between 14 and 75 per cent of patients[10–13,38], with some authors reporting a high incidence of incontinence to liquid stool[12,13]. There is only one report[14] of the treatment of anismus with injection of *C. botulinum* type A neurotoxin. Of seven cases, four patients had a successful outcome but two became incontinent.

Initial success following biofeedback may deteriorate over time, as is the case with incontinent patients[39]. Some studies have suggested that improvements in stool frequency do not persist at 6 months' follow-up[21] and others report the use of booster sessions of biofeedback to maintain success[20,40]. These findings emphasize the need for long-term follow-up studies of biofeedback therapy, as suggested by Enck[41], but as yet no large cohort of adult patients has been investigated.

Although biofeedback was completely successful in only 35 per cent of all patients, complete success was achieved by 63 per cent of patients who finished the prescribed treatment course. Although age, sex, duration of symptoms and presence of rectal pain did not influence outcome, willingness to comply with treatment protocols was the most important predictor of success. The ideal patient for biofeedback must be willing to spend as much time as necessary alleviating the symptoms. Such cooperation will be met with a success rate of more than 60 per cent without any morbidity.

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Assessment of ischaemia of the distal part of the gracilis muscle during transposition for anal dynamic graciloplasty

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Background Dynamic graciloplasty is used to create a neosphincter in patients with intractable faecal incontinence. When mobilizing the distal gracilis muscle from the upper leg, the minor vascular pedicles have to be ligated. This can interfere with the vascular supply in this part of the muscle.

Methods The arterial anatomy within the muscle was visualized by means of angiography of 11 post-mortem specimens. To quantify potential acute ischaemia, blood flow in the distal gracilis muscle was measured in ten patients with laser Doppler flowmetry during mobilization of the muscle.

Results Angiography showed that the main vascular pedicle and all minor pedicles drain into one and the same arterial system. After clamping of the minor vascular pedicles, blood flow (mean 25·8 (range 6·5–74·3) perfusion units) did not differ from values obtained before clamping (mean 25·4 (range 7·5–68·7) perfusion units). After a mean of 1·8 years, all muscles were vital. No correlation existed between the change in muscle blood flow and either squeeze pressure ($r = -0{\cdot}2$) or functional outcome ($r = 0{\cdot}31$).

Conclusion This study provides direct anatomical and physiological evidence of one arterial system within the gracilis muscle. It is therefore questionable whether ligation of the minor vascular pedicles is the bottleneck in human dynamic graciloplasty. An additional operation for vascular delay may be redundant. A prospective randomized clinical study should be performed to compare the functional outcome in patients with and without a delay procedure.

Anal dynamic graciloplasty is a successful treatment for patients with intractable faecal incontinence[1,2]. In this technique, the gracilis muscle is mobilized from the upper leg and wrapped around the anal canal with intact proximal neurovascular supply. In a second procedure, intramuscular electrodes and a pulse generator are implanted to activate the graciloplasty independently of volition. In about one-quarter of patients this treatment fails. Complications with the technique[1], infection and constipation[3] are the main reasons for failure. In 6 per cent there is insufficient contraction of the distal part of the gracilis muscle, the part essential for closure of the anal canal.

The blood supply of the gracilis muscle is from the major vascular pedicle, descending from the profunda femoris perforator artery, and one to four minor pedicles, descending from the superficial femoral artery. Gracilis muscle mobilization may induce ischaemia of the distal part of the muscle because it requires ligation of the minor vascular pedicles (*Fig. 1*). Other possible causes of a compromised blood flow are muscle transposition and continuous electrical stimulation Ischaemia can interfere with the clinical results because it may provoke fibrosis or even necrosis of the distal gracilis muscle. An additional vascular delay procedure (ligation of the minor vascular pedicles several weeks before transposition) may be indicated to allow development of collateral vessels[4].

The influence of ligation of the minor vascular pedicles on blood flow in the distal gracilis muscle was investigated. The arterial anatomy within the muscle was visualized. To quantify potential acute ischaemia, capillary flow before and after ligation was assessed by peroperative measurement with laser Doppler flowmetry. In addition, changes in muscle blood flow were correlated with the functional outcome approximately 2 years after transposition.

Patients and methods

Eleven post-mortem gracilis specimens from six subjects with a mean age of 69 (range 30–89) years were dissected free from the surrounding tissue. The major vascular pedicle and all minor pedicles were cannulated. The muscles were placed on an

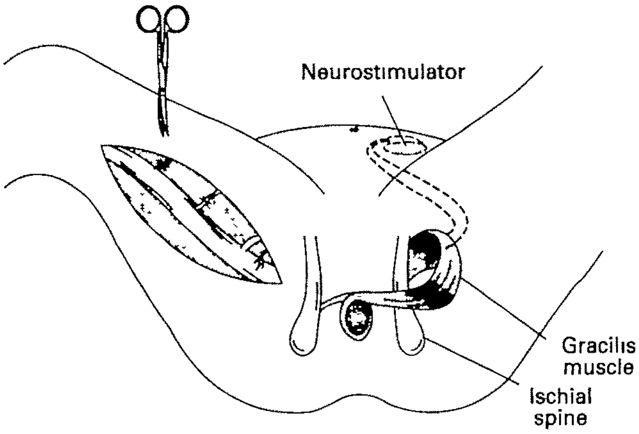

Fig 1 On the right side of the patient, mobilization of the gracilis muscle by ligation of the minor vascular pedicles is shown. Proximally, the major vascular pedicle and the obturator nerve with its branches are located On the left side, the dynamic graciloplasty configuration is shown after transposition of the muscle and implantation of the stimulation devices

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imaging table and radiocontrast (Isopaque 350; Nycomed Imaging, Oslo, Norway) was injected into the main pedicle under continuous imaging (Diasonic 9600, OEC Medical Systems, Salt Lake City, Utah, USA). Then, after real-time subtraction, radiocontrast was injected into the minor pedicles.

In ten consecutive patients (mean age 40 (range 18–62) years) undergoing graciloplasty for faecal incontinence, blood flow was assessed in the distal part of the gracilis muscle by means of laser Doppler flowmetry[5,6], before and after clamping all minor vascular pedicles. All ten patients had a normal electromyogram of the gracilis muscle. Measurements were performed with a commercially available system (Periflux PF3 monitor with a PF302 needle probe; Perimed, Stockholm, Sweden). An output of 1 V was calibrated against 100 perfusion units. The analog output from the laser Doppler flowmeter device was digitized by an analog to digital converter and subsequently stored on hard disk Off-line analysis was performed with a software program developed in the authors' institute Following introduction of the needle probe 5 cm proximal from the distal tendon of the gracilis muscle, basal blood flow was measured (5-min recording) after stabilization of blood flow for at least 5 min. All minor vascular pedicles were clamped, after which muscle blood flow was allowed to stabilize for at least 5 min. Then, muscle blood flow was again assessed for 5 min. This procedure was repeated three times for each muscle. From these laser Doppler flow readings, mean basal blood flow before and after clamping of all minor vascular pedicles was calculated.

Functional outcome was judged by anal manometry and by clinical results. Anal manometry was performed with a Konigsberg catheter (Konigsberg Instruments, Pasadena, California, USA), connected to a computer-assisted polygraph (Synectics Medical, Stockholm, Sweden). Continence was classified from 1 to 5 according to a standardized scoring method as described by Williams *et al*[4]: 1, continence to solids, liquids and flatus; 2, continence to solids and liquids but not to flatus; 3, continence to solids but occasional episodes of liquid incontinence; 4, occasional episodes of incontinence of solids; and 5, frequent episodes of incontinence of solids and liquids. Only patients with a score of 1 or 2 were considered continent and thus as having had a successful operation.

Data are presented as mean(s.d.). Statistical analysis was performed with the Wilcoxon matched-pairs signed-rank test, and correlation was tested with the Spearman correlation coefficient. $P<0.05$ was considered statistically significant. The studies were approved by the medical ethics committee of Maastricht University Hospital.

Results

The mean number of minor pedicles in the post-mortem specimens was 2 (range 1–3). In several muscles the smallest minor pedicle, often located at the transition from muscle to tendon, was too small to be cannulated and even after successful cannulation the contribution of this pedicle to muscular blood supply was negligible. After radiocontrast injection of the major pedicle, a mean of 2 ascending (smaller) and 3 descending branches (2 large, 1 small) became visible parallel to the muscle fibres and giving off smaller branches that traversed the muscle. The largest descending branch connected to all minor pedicles and injection of it filled all cannulas with contrast, suggesting the existence of one large arterial system. This was confirmed when radiocontrast was injected at the site of a minor pedicle, in which case the whole system was filled as well (*Fig. 2*).

The mean number of minor pedicles in the patients operated on was 2 (range 1–4). Blood flow in the distal part of the gracilis muscle, as assessed after clamping of the minor vascular pedicles (mean 25·8 (range 6·5–74·3) perfusion units) did not differ from values obtained before clamping (mean 25·4 (range 7·5–68·7) perfusion units) (*Table 1*). Percentage change in muscle blood flow following clamping was also not significant ($P=0.33$). There were considerable individual differences in basal blood flow and in the change of flow after clamping (*Table 1*).

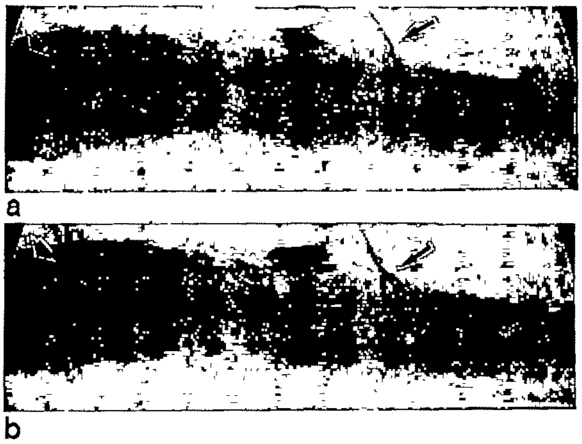

Fig. 2 Angiography of the gracilis muscle in post-mortem material. a Radiocontrast is injected in the main vascular pedicle (broad arrow) and the arterial system within the muscle, including the minor vascular pedicle (small arrow), is filled. b After real-time subtraction, radiocontrast is injected in the minor vascular pedicle (small arrow) and the same system, including the main vascular pedicle (broad arrow), is filled again

Table 1 Number of minor vascular pedicles, blood flow and outcome of graciloplasty in ten patients

Patient no.	No. of minor vascular pedicles	Blood flow (perfusion units)* Before clamping	Blood flow (perfusion units)* After clamping	Percentage fall in blood flow	Continence score†
1	1	7·5(0·1)	6·5(0·2)	13·3	2
2	2	26·9(5·2)	30·2(17·3)	−12·3	2
3	2	46·2(23·8)	36·8(20·2)	20·3	2
4	1	28·9(5·8)	30·1(5·5)	−4·2	1
5	1	19·4(2·7)	18·6(3·2)	4·1	2
6	4	16·4(5·6)	6·9(1·9)	57·9	2
7	2	19·0(9·6)	29·5(24·7)	−55·3	2
8	3	34·2(0·0)	36·8(3·4)	−7·6	1
9	1	68·7(6·0)	74·3(12·8)	−8·2	5‡
10	3	12·6(9·4)	9·1(2·5)	27·8	2

*Values are mean(s.d.), †according to the Williams incontinence classification[4]; ‡failure of the technique due to an unrelated cause

After a mean(s.d.) of 1·8(0·2) years, all muscles were vital and none of the patients suffered from postoperative complications such as perineal sepsis. After training by electrical stimulation, the mean(s.d.) pressure was 54(20·6) mmHg at rest, 180(61·6) mmHg during active contraction and 110(31·5) mmHg during electrical stimulation. No correlation existed between the change in muscle blood flow and either squeeze pressure ($r=-0.2$) or functional outcome ($r=0.31$).

Discussion

Ligation of the minor vascular pedicles, 5 weeks before the muscle is transposed, is a method used to prevent the development of fibrosis or necrosis of the distal part of the gracilis muscle. It is supposed that this procedure produces mild ischaemia in the distal part of the muscle, even if the muscle remains *in situ* and is not yet subjected to electrical stimulation. Consequently collateral vessels may develop to guarantee an adequate blood supply at the time the muscle is transposed and electrically stimulated. Angiography of the post-mortem specimens in this study demonstrated that one large arterial system exists within the muscle. This confirms previous findings[7]. The laser Doppler flowmetry data indicated that clamping of the minor vascular pedicles does not impair blood flow in the distal part of the gracilis muscle. This finding argues against the hypothesis that ligation of these pedicles is responsible for ischaemic changes. Moreover, the present study demonstrated that no correlation exists between changes in muscle blood flow following clamping and either contraction force or functional outcome.

Various factors may be responsible for damage of the muscle. Mobilization requires division of the distal tendon and the minor vascular pedicles. Tenotomy has been reported to produce a 33 per cent reduction in muscle mass leading to a 30 per cent reduction in maximum absolute power[8]. Muscle ischaemia may be the result of an insufficient microcirculation after ligation of the minor pedicles, but it may also be caused by transposition of the muscle around the anal canal under too much tension or by chronic electrical stimulation. When the muscle is transposed around the anal canal, the loss of normal resting tension may induce an increase in the connective tissue component of the muscle[9]. This was found to be the single most damaging intervention[10]. When stretch is applied to the muscle, connective tissue accumulation can be prevented and protein synthesis is induced to prevent atrophy[11]. Too much stress, however, can produce compression of the vascular pedicle and thereby impair muscle blood flow. Little is known about problems that can arise from impaired venous or lymph drainage. Mobilization of the muscle certainly damages lymph vessels in the thigh, necessitating the use of tight stockings for several weeks to prevent oedema in the leg. Impaired lymph drainage within the transposed muscle may cause swelling and complicate normal blood flow. After transposition, there is a 33 per cent decrease in muscle diameter[12]. Despite the atrophy, the muscle remains forceful enough to close the anal canal. It is clear that many factors are involved in the development of muscle damage; they all exert an additive effect on one another, and there is strong theoretical support for the view that it may be advisable to give extra protection at the moment most damage is inflicted on the muscle.

Laser Doppler flowmetry provides an accurate measure of muscle blood flux. The present observations indicate that ligation of the distal vascular pedicles does not compromise blood flux within the distal part of the gracilis muscle. This finding is in line with the long-term functional outcome. Given these data, it is questionable whether ligation of the minor vascular pedicles makes a significant contribution to blood flow or muscle function in human dynamic graciloplasty. The possible value of vascular delay may be increased if the muscle is challenged by electrical stimulation, but this can be technically difficult.

The experimental data from this study question the value of a vascular delay procedure. To investigate the clinical effect of the procedure, a prospective randomized trial to compare the outcome in patients with and without vascular delay is necessary. Given the anatomical and physiological differences between patients, a group that could benefit from vascular delay might then be selected for this procedure.

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Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer

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Background The purpose of the present study was to investigate whether a 1-month regimen of postoperative radiotherapy combined with 5-fluorouracil could reduce the local recurrence rate and improve survival in patients with Dukes B and C rectal cancer.

Methods One hundred and forty-four patients were randomized to surgery alone or surgery combined with postoperative radiotherapy (46 Gy) and bolus 5-fluorouracil 30 min before six of the radiotherapy fractions. One hundred and thirty-six patients were eligible.

Results The adjuvant treatment was well tolerated. After an observation time of 4–8 years, patients in the adjuvant treatment group had a cumulative local recurrence rate of 12 per cent compared with 30 per cent in the group that had surgery only ($P = 0{\cdot}01$). The 5-year recurrence-free and overall survival rate was 64 per cent in the adjuvant group compared with 46 per cent ($P = 0{\cdot}01$) and 50 per cent ($P = 0{\cdot}05$) respectively in the surgery group. The adjusted relative risk of recurrence and death for the adjuvant group was 0·48 (95 per cent confidence interval 0·28–0·82) and 0·56 (0·33-0·94) respectively.

Conclusion The 1-month postoperative combination regimen improved treatment results in patients with Dukes B and C rectal cancer, in terms of local recurrence rate, recurrence-free survival and overall survival, without serious side-effects.

Adjuvant treatment for operable rectal cancer has traditionally been radiotherapy based, because of a serious problem with local recurrence. Preoperative as well as postoperative radiotherapy have been shown to reduce local recurrence rate, but so far no survival benefit has been documented in the literature[1–9].

In 1985–1986 the Gastrointestinal Tumor Study Group (GITSG) in the USA[10,11] demonstrated an improvement in disease-free survival and overall survival compared with surgery alone by combining postoperative radiotherapy and combination chemotherapy with 5-fluorouracil and methyl-CCNU for 18 months. However, this regimen was not well tolerated, as only 30 of the 46 patients completed treatment as scheduled, and the toxicity was considerable. In the Mayo/NCCTG trial[12], in which patients were randomized between a more optimal radiation regimen in one arm and the combination of radiotherapy and chemotherapy for 6 months in the other, the combined treatment reduced the local and distant recurrence rate and improved survival significantly compared with radiotherapy as adjuvant treatment. About 20 per cent of patients in the combination group had severe diarrhoea and leucopenia.

In a recent report of a North Central Cancer Treatment Group (NCCTG)/Intergroup trial, O'Connell *et al.*[13] demonstrated that the combined chemoradiotherapy can be improved with respect to both relapse-free and overall survival by administering 5-fluorouracil continuously during the radiotherapy period, with a moderate increase in the incidence of severe diarrhoea. Moreover, methyl-CCNU was found not to be of any importance, as was also indicated by the GITSG[14].

The present study was initiated in 1986–1987 at a time when only one randomized trial had shown a benefit of postoperative radiotherapy and chemotherapy[10]. The aim of this study was to investigate the effect of an optimized radiotherapy regimen combined with concurrent short-term 5-fluorouracil only during the radiotherapy period (1 month), given 30 min before irradiation to obtain maximum radiosensitization.

Patients and methods

Patients

Eligible patients had histologically confirmed adenocarcinoma of the rectum and had undergone 'radical' resection with curative intent The tumour was located less than 18 cm from the anal verge. Abdominoperineal resection or low anterior resection was performed at the surgeon's discretion. Transposition of omentum to the pelvis was recommended. Patients with Dukes B disease (growth through the entire bowel wall) or Dukes C lesions (lymph node metastases) were included. Patients aged more than 75 years were included only if they were fit. All patients had Eastern Cooperative Oncology Group scores before surgery of 0–1 Patients with other previous or concurrent malignant disease (except for basal cell carcinoma of the skin) were excluded. The adjuvant treatment had to be started less than 8 weeks after operation (preferably 4–6 weeks after).

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Randomization

The trial was approved by the regional ethics committee before recruitment of patients started. After informed consent had been given the patients were randomized either to operation alone or adjuvant postoperative treatment. They were stratified according to treatment hospital.

Treatment

Patients assigned to postoperative adjuvant treatment received radiotherapy to the posterior part of the pelvis by a three-field technique with one posterior and two opposed lateral portals. The superior border of the treatment volume was the sacral promontory (L5–S1 intervertebral space); the inferior was the perineum in all cases. The lateral border of the posterior field was 1·5 cm lateral to the bony margin of the true pelvis. The anterior border of the lateral fields was the centre of the femoral heads and approximately 2 cm anterior to the promontory, whereas the posterior border was located posterior to the sacrum. Photon energies of 10–16 MV were required. The patients were treated in the prone position, and patients were strongly recommended to have a full bladder during treatment. This technique was chosen as the result of a preliminary investigation of localization of bowel with computed tomography (CT) after peroral contrast in a series of patients in the prone position with full bladder gave the smallest amounts of small bowel within the treatment volume. A fraction of 2 Gy, with all fields being treated every day, was given 5 days a week up to 46 Gy (23 fractions in 4·5 weeks).

Chemotherapy with 5-fluorouracil was given on the days of radiotherapy fractions 1, 2, 11, 12, 21 and 22. A dose of 500 or 750 mg was given when the patient's surface area was less than or more than 1·75 m^2 respectively. The cytotoxic agent was given as a bolus infusion/injection 30 min before irradiation started.

Patient follow-up

During the radiotherapy–chemotherapy period symptoms and signs of acute toxicity were noted, and a physical examination as well as blood chemistry were performed every week. The first follow-up after treatment was performed 3 months after operation in both groups of patients, and included a clinical examination, blood tests including measurement of liver enzymes and carcinoembryonic antigen level, chest radiography, liver ultrasonography and CT of the pelvis as a baseline examination. The clinical examination included rigid sigmoidoscopy and vaginal examination, when possible. Follow-up was 3 monthly for the first 2 years after surgery, and every 6 months thereafter. Each follow-up included the same examinations as the 3-month follow-up, except for the CT which was performed at 9, 15 and 24 months in addition to the baseline examination.

A local recurrence was defined as a pelvic recurrence between the levels of the sacral promontory and the perineum, whereas other recurrences were classified as distant metastases. If recurrent disease was suspected on the basis of symptoms and/or investigations performed, histological or cytological confirmation was recommended, although not mandatory.

Statistical analysis

The main objectives of the protocol were to investigate whether the adjuvant treatment could reduce the local recurrence rate from approximately 40 to 20 per cent and improve the 5-year survival rate from 40 to 55 per cent, with a significance level of $P = 0·05$ and power of 0·80. It was calculated that 270 patients were required to show this survival difference. Recruitment was terminated when 144 patients had been included, because of slow recruitment. No interim analyses were performed.

For two-way frequency tables Pearson's χ^2 test of independence or, when the expected number was 20 or less, Fisher's exact test (two-tailed) was used. The probabilities of surviving were calculated with the Kaplan–Meier product-limit method. The differences between the survival curves were tested by the log rank test[15]. To adjust for multiple comparisons the Bonferroni correction (multiplying the *P* values with number of tests) was used[16]. The Cox proportional hazards model was used to estimate the relative risk of relapse and death taking into account other prognostic factors[17]. The BMDP (Los Angeles, California, USA) statistical software was used[18].

Results

Between 1987 and 1991, 144 patients were randomized, 72 to surgery only and 72 to surgery plus adjuvant postoperative radiotherapy and chemotherapy. Eight patients were found to be ineligible, of whom two had Dukes stage A and one Dukes D disease, one had prostate cancer (not rectal cancer) and four had previous or concurrent other malignant disease. The characteristics of the 136 eligible patients are given in *Table 1*. Of the 66 patients in the adjuvant group, seven did not receive the radiotherapy and chemotherapy, three because of postoperative complications, two who were not referred to radiotherapy (surgeon's decision) and two because the patient refused after initial consent. These patients were all included in the analyses.

Of the 59 adjuvant-treated patients, 42 received a 5-fluorouracil dose of 750 mg, and 17 received 500 mg. Four patients had protocol violations: two received a reduced radiation dose (36 and 38 Gy) combined with only four 5-fluorouracil injections, and two received 50 Gy because of a two-week split. These patients were all included in the analyses.

Toxicity

The acute toxicity in patients receiving radiotherapy and chemotherapy is given in *Table 2*. No treatment-related deaths were seen, and the acute toxicity was in general mild or negligible. World Health Organization grade 3 toxicity was observed in only three patients with pronounced skin reactions in the perineal and external genital regions. Diarrhoea was rather mild and did not require intravenous fluids or hospital management. No troublesome bone marrow toxicity was found (one patient had a white cell count of $2·6 \times 10^9$ per litre). The two patients who received a reduced radiation dose, and the other two who had a split course, had a dermatitis grade 3 or combined dermatitis grade 2–3 and diarrhoea grade 2.

With respect to delayed complications, five patients have been operated on for small bowel obstruction (4 per cent). Two of these were in the surgery only group, and

Table 1 Characteristics of patients recruited

	Surgery	Surgery and adjuvant
No. of patients randomized	72	72
No. of eligible patients	70	66
Sex ratio (M:F)	40:30	42:24
Median (range) age (years)	65 (39–78)	63 (38–77)
Type of resection		
Abdominoperineal	28	30
Low anterior	42	36
Dukes stage		
B	39	31
C	31	35

three in the adjuvant group. Two more patients, one in each group, had periods of obstruction symptoms but did not require laparotomy. No other serious treatment-related complications were observed.

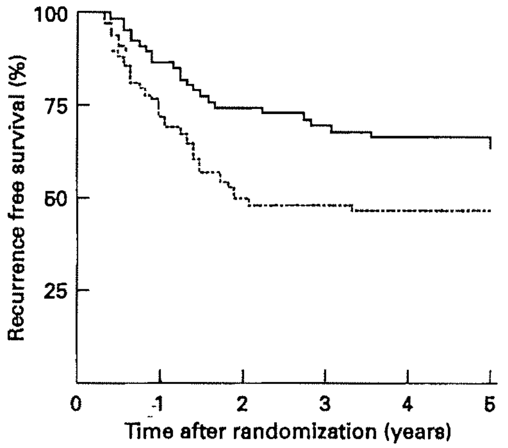
Recurrence

After an observation time of 4–8 years, the 5-year recurrence-free rate was 46 per cent in the surgery only group and 64 per cent in the adjuvant group ($P = 0·01$, relative improvement 37 per cent). The curves showing time to recurrence are shown in *Fig. 1*. The cumulative local recurrence rate (total local recurrences during the observation time) was 30 per cent in the surgery only group compared with 12 per cent in the adjuvant group ($P = 0·01$) (*Table 3*). Among patients who actually received the adjuvant treatment, the local recurrence rate was 10 per cent.

Table 2 Acute toxic reactions in 59 patients receiving radiotherapy and 5-fluorouracil

	Grade*			
Reaction	1	2	3	4
Nausea	7	5	0	0
Vomiting	2	1	0	0
Diarrhoea	12	8	0	0
Dermatitis	14	7	3	0
Anaemia	1	0	0	0
Leucopenia	17	1	0	0
Thrombocytopenia	0	0	0	0

*Classified according to World Health Organization criteria



o. at risk						
Adjuvant therapy	66	57	48	45	36	27
Surgery only	70	51	33	31	27	17

Fig. 1 Recurrence-free survival in patients treated with surgery and adjuvant therapy (———, $n = 66$) or surgery only (------; $n = 70$) $P = 0·01$ (log rank test)

In most cases the local recurrences were combined with distant metastases (*Table 3*). Local recurrences without distant metastases were found in only 2 per cent of patients in the adjuvant group and 13 per cent of those in the surgery group ($P = 0·01$). The number of patients who developed distant metastases during the observation period was not statistically different between the two groups (39 per cent in the surgery only group *versus* 33 per cent in the adjuvant group).

By univariate analysis, adjuvant therapy as well as low anterior resection as the surgical method predicted a favourable prognosis with respect to relapse (*Table 4*). By Cox regression analysis, it was found that none of the potential prognostic factors such as Dukes stage, sex, age and surgical method could explain the differences observed between the two treatment groups. However, as shown in *Table 5*, the type of operation performed was an independent determinant of recurrence. Thus, patients undergoing abdominoperineal resection had a higher risk of recurrence than those who had low anterior resection. Dukes stage, age and sex were not found to be of significant importance for recurrence. The unadjusted relative risk of recurrence for the adjuvant group was 0·54 (95 per cent confidence interval (c.i.) 0·32–0·91), whereas the adjusted relative risk of recurrence for this group was 0·48 (0·28-0·82) (*Table 5*).

Survival

Survival curves for the two treatment groups are shown in *Fig. 2*. The 5-year overall survival rate was found to be 50

Table 3 Cumulative recurrence in patients treated with surgery or surgery and adjuvant therapy

	Surgery ($n = 70$)*	Surgery and adjuvant ($n = 66$)*	Difference (%)†	P‡
Local recurrence	21 (30)	8 (12)	18 (5–31)	0·01
Local recurrence only	9 (13)	1 (2)	11 (2–20)	0·01
Distant metastasis	27 (39)	22 (33)	6 (0–22)	0·52
Distant metastasis only	15 (21)	15 (23)	− 2 (0–16)	1·00

Total recurrences observed during the observation time are indicated. Values in parentheses are *percentages or †95 per cent confidence intervals. ‡Fisher's exact test

Table 4 Univariate analysis of recurrence-free survival and overall survival

	5-year recurrence-free survival (%)			5-year overall survival (%)		
Variable	Not present	Present	P*	Not present	Present	P*
Adjuvant therapy	46	64	0·01†	50	64	0·05
Abdominoperineal resection	64	43	0·02	73	47	0·005†
Dukes C disease	60	49	0·08	67	53	0·03
Female sex	55	55	0·99	55	67	0·47
Age > 70 years	56	48	0·60	62	54	0·74

*Log rank test; †significant after adjustment for multiple comparisons with the Bonferroni method

Table 5 Relative risk of recurrence and death according to prognostic variables

	Relative risk of recurrence*	Relative risk of death*
Adjuvant treatment *versus* surgery only	0·48 (0·28–0·82)	0·56 (0·33–0·94)
APR *versus* low AR	1·85 (1·11–3·11)	1·88 (1·11–3·10)
Dukes stage C *versus* B	1·63 (0·97–2·73)	1·78 (1·06–2·99)

*Adjusted for other factors (Cox regression analysis). Values in parentheses are 95 per cent confidence intervals. APR, abdominoperineal resection; AR, anterior resection

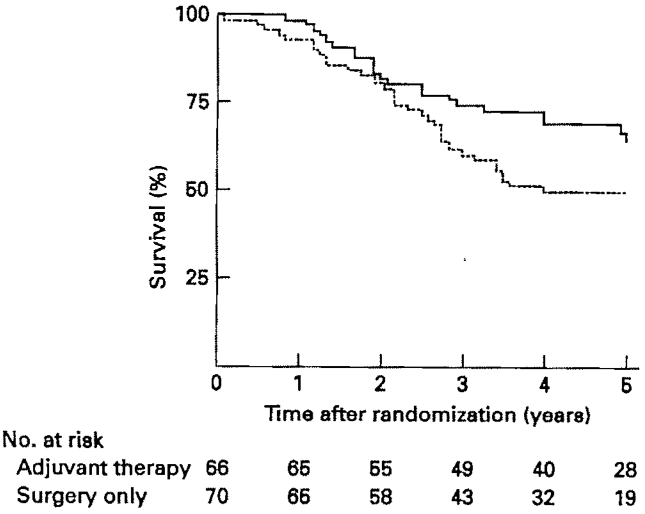


Fig. 2 Overall survival in patients treated with surgery and adjuvant therapy (———, $n = 66$) or surgery only (-----, $n = 70$). $P = 0{\cdot}05$ (log rank test)

per cent for the surgery only group and 64 per cent for the adjuvant group ($P = 0{\cdot}05$). The relative improvement was 29 per cent. The unadjusted relative risk of death for the adjuvant group was 0·60 (95 per cent c.i. 0·36–1·02). By univariate analysis, adjuvant therapy, low anterior resection and Dukes B disease predicted a favourable prognosis with respect to survival (*Table 4*). Sex and age did not influence survival. By Cox regression analysis none of the potential prognostic factors (Dukes stage, sex, age and surgical procedure) could explain the differences observed between treatment groups. However, as shown in *Table 5*, Dukes stage as well as type of surgery were found to be independent prognostic factors. Thus, patients with Dukes C tumours and those who had abdominoperineal resection had higher relative risk of death than patients with Dukes B tumours and those undergoing low anterior resection. The adjusted relative death risk for the adjuvant group was 0·56 (95 per cent c.i. 0·33–0·94) (*Table 5*).

Discussion

The present study has demonstrated in Dukes B and C rectal cancer that a postoperative radiotherapy regimen combined with 5-fluorouracil exclusively during the radiotherapy period reduces significantly the local and overall recurrence rate and improves survival, compared with surgery alone. Moreover, the regimen is well tolerated with low acute and long-term toxicity. The results are similar to those obtained by the GITSG with postoperative radiotherapy and 5-fluorouracil and methyl-CCNU for 18 months[10,11]. To the authors' knowledge the GITSG series is the only published study showing a survival benefit of postoperative radiotherapy and chemotherapy compared with surgery alone. However, a benefit with respect to both recurrence rate and survival was demonstrated in the Mayo/NCCTG trial with a 6-month combination regimen, when compared with radiotherapy as adjuvant treatment[12].

Recently, it has also been shown that methyl-CCNU is not an essential part of the chemotherapy regimen[13,14], and that continuous 5-fluorouracil during the radiotherapy period was more efficient than if the drug was given as a bolus[13]. The continuous 5-fluorouracil regimen improved the 4-year recurrence-free rate from 53 to 63 per cent and survival from 60 to 70 per cent. The present results are at the same level with respect to recurrence rate and survival.

The present study confirms that postoperative radiotherapy combined with 5-fluorouracil improves the outcome for patients with Dukes B and C rectal cancer. Importantly, it also demonstrates that this improvement can be obtained by a simple and less resource-demanding regimen with treatment for only 4·5 weeks. Moreover, this regimen is well tolerated with only minor acute and late toxicity. Of importance, no serious bone marrow and gastrointestinal toxicity was observed. The major reasons for this are probably the radiation treatment technique used (three fields, prone position and full bladder) and the small amounts of 5-fluorouracil given (500 or 750 mg six times).

Why is this simple short-term postoperative regimen with small 5-fluorouracil doses able to improve survival and reduce the recurrence rate? It is well documented that radiotherapy alone as adjuvant treatment may reduce the local recurrence rate to approximately one half the value obtained by surgery only[1–9]. However, radiotherapy without chemotherapy has so far not been shown to improve survival[1–9]. Against this background, it is conceivable that the small dose of 5-fluorouracil used in the present study really has a significant biological effect. The most important effect of 5-fluorouracil in the present regimen is probably its radiosensitizing effect, as the improvement was most pronounced with respect to local recurrences, although a systemic effect of 5-fluorouracil may also have taken place.

The interaction of 5-fluorouracil and irradiation in this context is of major importance[19–24]. This interaction has been studied primarily in tissue culture. Byfield *et al.*[21] found in cell line experiments that the drug should be given after irradiation to obtain radiosensitization. Other experiments[20,22,23] have shown that the optimal relationship may vary from cell line to cell line, and that it may be of importance to have 5-fluorouracil present in the cells during irradiation. One should, however, be cautious in the clinical interpretation of these data, as it is questionable whether results obtained on cell lines after a single and large radiation fraction are relevant in a clinical situation with fractionated therapy employing 1·8–2·0 Gy per fraction. If a major mechanism of radiosensitization is inhibition of repair of sublethal radiation damage[19,20] then it seems reasonable that 5-fluorouracil should be present in the cells at the time when this repair is at its maximum, i.e. just after the irradiation takes place. Recent measurement of concentrations of 5-fluorouracil and metabolites in human tumour tissue have shown the highest concentrations 30–90 min after a bolus injection[25]. It seems reasonable then to give 5-fluorouracil before irradiation when treating patients, and not after, which has usually been done in the previous trials of postoperative radiotherapy and bolus 5-fluorouracil.

In the present study 5-fluorouracil was given as a bolus 30 min before irradiation on fractions 1, 2, 11, 12, 21 and 22. This schedule was designed in the light of the theoretical considerations discussed above. The large reduction in the local recurrence rate and improved survival rate obtained using this regimen suggest that the time-scheduling of 5-fluorouracil and irradiation was optimized. Fortunately, the side-effects did not seem to be increased by the combination, as the limited toxicity observed is no more than that seen after radiotherapy alone.

A comparison between the present short-term time-scheduled combination regimen and radiotherapy with continuous 5-fluorouracil infusion in a future trial would be interesting. The effect of additional adjuvant chemotherapy, particularly on reduction of distant metastases, should be investigated. The addition of leucovorin during radiotherapy should also be tested. At present, the simple and less resource-demanding regimen with low toxicity seems highly competitive compared with the more commonly used combination regimens for the adjuvant treatment of high-risk rectal cancer.

It is of major interest that, although the present study shows a 5-year recurrence-free rate of 64 per cent, the Mayo/NCCTG study presents a corresponding figure of 58 per cent and the recent NCCTG/Intergroup trial has a 4-year recurrence-free rate of 63 per cent, the best published results are for surgery alone. Thus, MacFarlane *et al.* reported a 5-year recurrence-free rate of 78 per cent and a local failure rate of about 5 per cent after the use of total mesorectal excision (TME) in patients with Dukes B and C cancer[26]. The TME technique is currently being evaluated in a non-randomized setting in several other centres and also nationwide, particularly in Scandinavia. At present, the standard treatment of high-risk rectal cancer is therefore not settled, neither with respect to the surgical technique nor to the adjuvant treatment. However, on a background of a high local recurrence rate with surgery alone (20–30 per cent) and a poor 5-year survival rate (about 50 per cent), the combined short-term, time-scheduled and low-toxicity regimen reported here can be recommended in rectal cancer.

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Appendix

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Late results justify resection for multiple hepatic metastases from colorectal cancer

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Background Whilst hepatic resection is accepted for single colorectal metastases, the role of surgery for multiple deposits is less certain. This study reports results of a programme of aggressive resection of hepatic metastases.

Methods Of 150 hepatic resections for colorectal metastases, 107 patients have completed 1–9 years' follow-up for this actuarial survival analysis. Indications for resection were disease confined to the liver, resectability of all metastases and preservation of sufficient hepatic parenchyma.

Results One patient (1 per cent) died after operation and six (6 per cent) suffered serious complications (two surgical and four medical) but with full recovery. Patients who had a radical resection ($n = 89$) had 1- and 5-year survival rates of 94 and 37 per cent respectively. A palliative group ($n = 18$) with disease elsewhere ($n = 9$) or positive histological margins ($n = 9$) had corresponding survival rates of 56 and 6 per cent. Univariate analysis of the group who had radical surgery demonstrated that survival depended on size of metastases (less than 7 cm) ($P = 0{\cdot}014$), width of clear resection margin (greater than 5 mm) ($P = 0{\cdot}004$) and primary site ($P = 0{\cdot}010$). Factors not affecting outcome were number of metastases, unilateral *versus* bilateral disease, synchronous *versus* metachronous spread, tumour differentiation and Dukes stage. Multivariate analysis demonstrated independent survival advantage for small metastases (less than 7 cm) ($P = 0{\cdot}002$) and clear resection margin greater than 5 mm ($P = 0{\cdot}037$).

Conclusion Hepatic resection in selected patients with single and multiple colorectal hepatic metastases is justified.

The acceptance of surgical resection for colorectal metastases in the liver is based on two propositions. First, that hepatic resection can be performed safely without significant long-term morbidity and, second, that the pattern of spread from colorectal carcinoma includes some patients in whom metastatic spread is limited and confined to the liver.

In 1986 a programme was initiated in Basingstoke, based on the experience of Johannes Scheele in Erlangen, with the criteria that patients be treated by liver resection if metastatic disease was confined to the liver, all metastases were removable and at least one-third of the liver could safely be preserved. In this paper, the survival analyses of the first 107 patients followed for at least 1 year are reported.

Patients and methods

Between November 1986 and January 1996, 200 hepatic resections have been performed of which 150 were for colorectal metastases. One hundred and seven patients who had 114 resections have completed a 1-year follow-up and are the subjects of this survival analysis. One-third of the patients were referred from within Wessex and two-thirds from outside the region, principally from southern England Patients were initially assessed for operability if preliminary computed tomography (CT) was favourable and there was no evidence of local recurrence. A chest radiograph and CT of the chest were performed routinely together with more detailed analysis of the liver using computed aortoportography (CTAP) since 1990. This was supplemented when necessary by ultrasonography and, latterly, magnetic resonance imaging (MRI). If there was skeletal pain or neurological symptoms an isotope bone scan or CT of the brain was done Laparotomy was offered to patients with disease confined to the liver and in whom all nodules were technically removable At laparotomy, resectability was assessed in all patients by inspection for peritoneal disease, palpation and intraoperative liver ultrasonography. Nine patients not included in this study did not receive further operative treatment because of previously undetected peritoneal and/or nodal spread. One hundred and seven patients underwent 114 hepatic resections using techniques described previously[1].

The procedures were deemed radical or curative if the surgeon and histopathologist agreed that the tumour nodule was not breached and if there was no evidence of metastatic disease elsewhere. Patients in whom there was known unresectable disease elsewhere, or in whom the margin was breached, either macroscopically or microscopically, were grouped as palliative. All postoperative events were documented prospectively for any complications and graded for severity: 'slight' meaning no disruption to the expected recovery, 'relevant' implying delay in discharge, and 'life-threatening' requiring intensive medical or surgical intervention. All patients have been followed prospectively and documented for disease recurrence and death Patients are investigated at 6 months, 1 year and annually until death, by CT or ultrasonography of the abdomen and chest radiography with further investigation of specific symptoms. No patient has been lost to follow-up.

Survival analyses were carried out using the Kaplan–Meier method and checked for statistical significance using the log rank test or χ^2 test where appropriate. Univariate analysis was performed for the patients who had a curative resection The factors analysed by univariate analysis were then entered into a Cox proportional hazards model for multivariate regression analysis.

Results

Details of the 114 hepatic resections are summarized in *Table 1* Classical resections predominated but segment orientated resections ($n = 17$)[2,3] and atypical or wedge

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Table 1 Hepatic resections for colorectal metastases

Right hepatectomy	61*
Left hepatectomy	18†
Lateral segments II and III	6
Extended right hepatectomy	5‡
Extended left hepatectomy	1§
Monosegmentectomy	7
Bisegmentectomy	10
Atypical excision	2
Wedge excision	2
Multiple wedge excision	2
Total	114

*Nineteen with an additional procedure on the left side of the liver; †six with an additional procedure on the right side of the liver; ‡implies additional total removal of segment IV; §implies additional total removal of segments V and VIII

Table 2 Additional procedures to hepatectomy done in 24 patients

Anterior resection*	1
Colon resection*	2
Diaphragm resection	7
Nephrectomy, colon and diaphragm resection	1
Biliary reconstruction and diaphragm resection	1
Biliary reconstruction	1
Biliary reconstruction and vena cava graft	1
Sleeve resection of the duodenum	1
Block dissection of lesser sac	1
Partial nephrectomy† and splenectomy	1
Nephrectomy†	1
Cholecystectomy	4
Repair of incisional hernia	1
Aortic aneurysm repair	1

*Synchronous resection of colorectal carcinoma, †synchronous resection of primary renal carcinoma

excisions ($n = 6$) were used, particularly in the elderly or in redo cases to preserve hepatic parenchyma and thereby avoid postoperative hepatic failure. Twenty-four patients had additional operative procedures as outlined in *Table 2*. In only one was this additional procedure for discontinuous colorectal spread (block dissection of lesser sac), although 12 patients underwent *en bloc* resection for local invasion to nearby structures. Of the 107 patients, 89 (83 per cent) were deemed to have had radical surgery and 18 (17 per cent) palliative, nine because of non-resectable disease elsewhere and nine with positive margins. Of the nine patients with non-resectable disease, four had deposits known before operation (one lung, one pelvis, one local, one liver) and five had unexpected disease discovered at laparotomy (two peritoneal, one nodes in porta hepatis, two in liver).

Morbidity and mortality rates

Of the 114 hepatic resections, one patient died in hospital, giving an in-hospital and 30-day mortality rate of 1 per cent. This deeply jaundiced patient (bilirubin level 616 μmol/l) had an extended right hepatectomy with Roux loop biliary reconstruction and died within 1 week from hepatic insufficiency. Three patients (3 per cent) had surgical complications: one had a small volume biliary leak which was treated conservatively; one bled from a jejunal Roux loop anastomosis after operation and required laparotomy and under-running of a small artery; and one patient developed hepatic insufficiency following extended right hepatectomy further complicated by an ischaemic stricture of the left hepatic duct which needed operative Roux loop biliary diversion.

Post-operative medical complications occurred in 18 patients (17 per cent) and were deemed life-threatening in two, relevant in two and slight in 15. One patient was successfully resuscitated following cardiac arrest from a massive pulmonary embolism, one developed atrial fibrillation which required cardioversion and two patients had prolonged hepatic insufficiency which was life-threatening in one. Minor complications included chest infection ($n = 6$), small bowel paralytic ileus ($n = 3$), urinary retention ($n = 2$), urinary tract infection ($n = 1$), mild hepatic insufficiency ($n = 1$), minor sacral sore in a paraplegic patient ($n = 1$) and possible small pulmonary embolus ($n = 1$). In total, six patients had serious or significant morbidity (6 per cent), including two surgical and four medical complications. There were no longer term complications in any patients.

Mean blood loss for the 114 resections, inclusive of 24 additional operations, was 989 (range 75–10 000) ml with a mean hospital transfusion rate of 1·75 (range 0–22) units. The single patient with massive blood loss had simultaneous partial nephrectomy of a solitary kidney complicated by profuse bleeding from a splenic tear. For the last 50 resections in the group, mean blood loss was 436 (range 75–1700) ml and the mean amount of blood transfused was 0·16 (range 0–4) units. The median hospital stay was 11 (range 6–73) days.

Survival

All patients were followed up prospectively and no patient has been lost. Survival for the whole group was 87 per cent at 1 year, 47 per cent at 3 years and 30 per cent at 5 years. Corresponding figures for patients considered to have radical resection were 94, 56 and 37 per cent, and for the palliative group 56, 11 and 6 per cent.

Univariate analysis. In patients who had a radical resection, increased size of the hepatic lesion affected the outcome adversely using less than 7 cm as the cut-off point (*Fig. 1*). Moreover, five of the 22 patients with metastases greater than 10 cm (mean diameter 13 cm) had

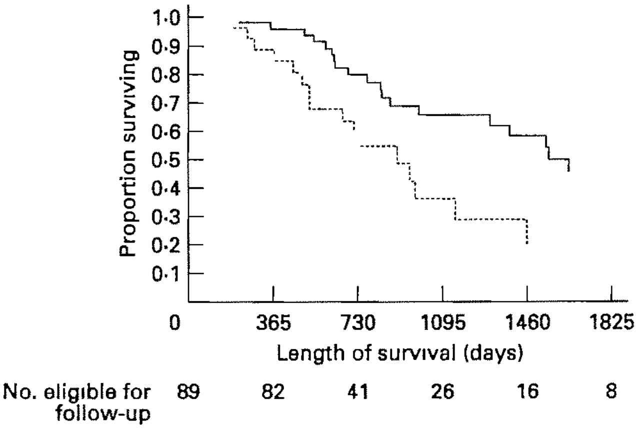

Fig. 1 Five-year survival after radical resection of metastases less than 7 cm (——, $n = 60$ patients) or greater than 7 cm (…. , $n = 29$) ($P = 0.014$), log rank test

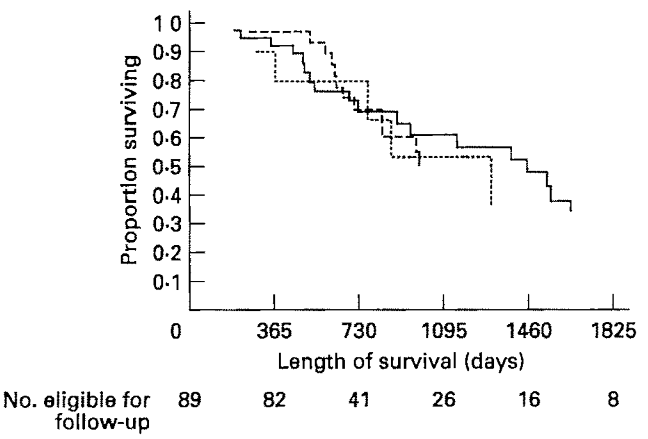

Fig. 2 Survival pattern in patients with solitary metastases resected (———, $n = 41$), patients with two or three metastases removed (– – –, $n = 35$) and patients with more than three metastases removed (....., $n = 13$) ($P = 0{\cdot}882$), χ^2 test

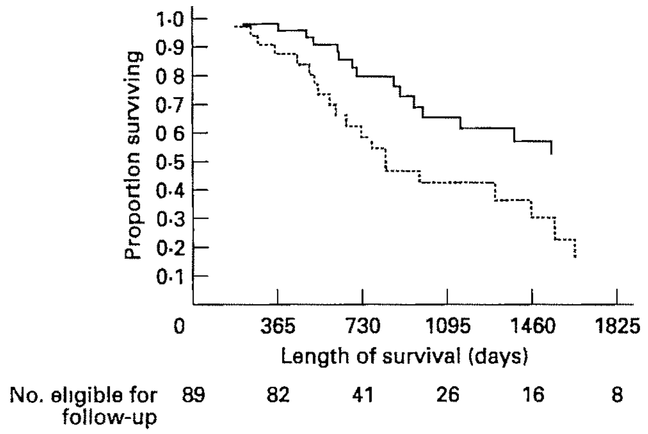

Fig. 3 Survival in patients with a disease-free resected margin of 5 mm or greater (———, $n = 54$) and in those with a margin of 0–4 mm (......, $n = 35$) ($P = 0{\cdot}004$), log rank test

positive margins on histology. The number of metastases removed had no significant effect on survival (*Fig. 2*). A small group of patients ($n = 13$) with four or more metastases fared as well as patients with solitary tumours ($n = 41$) or two to three metastases ($n = 35$).

Patients who had resection of bilateral disease ($n = 18$) fared less well than those with disease confined to one side of the liver ($n = 71$). The respective 5-year survival rates of 14 and 41 per cent were not significantly different ($P = 0{\cdot}057$).

A wider margin of normal tissue in the resected specimens did confer survival benefit (*Fig. 3*). By contrast, three patients who had only an intact capsule preserved and no margin had 1- and 3-year survival rates of 100 and 67 per cent with the longest survivor currently at 4·3 years.

Neither the histological differentiation nor the involvement of lymph nodes in the primary tumour had an effect on long-term survival. The 5-year survival rate in patients with well differentiated ($n = 26$), moderately differentiated ($n = 53$) and poorly differentiated ($n = 9$) tumours was 55, 29 and 39 per cent respectively ($P = 0{\cdot}330$). Similarly, 36 patients with Dukes A and B disease initially had a 5-year survival rate of 33 per cent compared with 40 per cent for 53 patients with Dukes C lesions ($P = 0{\cdot}425$). The site of the primary tumour affected outcome; right-sided colonic tumours fared less well. Five-year survival rates for right ($n = 15$), left ($n = 29$) and rectal ($n = 44$) tumours were 27, 35 and 42 per cent respectively ($P = 0{\cdot}010$).

Finally, survival was not related to whether the disease was synchronous or metachronous. Thirty-six patients who had liver resection within 3 months of the primary bowel procedure had a 25 per cent 5-year survival rate compared with 45 per cent in 53 patients with disease discovered during follow-up ($P = 0{\cdot}081$).

Multivariate analysis. Multivariate regression analysis demonstrated two favourable factors. Survival was improved if the size of the metastasis was less than 8 cm ($P = 0{\cdot}002$) and if the resection margin was greater than 5 mm ($P = 0{\cdot}037$). No other feature contributed to crude survival.

Pattern of recurrence

Of the 89 patients who had curative surgery, 39 have subsequently died and 22 others who are alive have developed recurrent disease. The liver was involved with recurrent disease in 34 patients. In 25 patients (41 per cent), the liver alone was affected and seven patients (11 per cent of total recurrences) have now had a further resection. All are alive, one with disease and six free from disease 6 months to 7 years after reresection. The liver and lung were involved together in seven cases and one patient underwent subsequent resection of both pulmonary and hepatic deposits. In two others the liver was involved as a multisite recurrence. The lungs were involved as isolated organ recurrence in nine patients (15 per cent) and one patient underwent pulmonary resection. Eighteen patients presented with recurrent disease not involving the liver and lungs. Intra-abdominal or peritoneal recurrence occurred twice and three patients had local recurrence at the site of primary resection. Three patients had isolated cerebral metastases; one presented 5 years following hepatic resection. One patient had ovarian metastases and nine others had widespread dissemination.

Discussion

Liver surgery can now be performed with the same risk and morbidity associated with other major procedures[4–6]. These results have confirmed the suggestion of others that hepatic resection is effective in selected patients with colorectal metastases[7–13], even in the elderly[14].

Selection of the suitable patient requires further study. Inability to identify accurately the full extent of metastatic spread remains the biggest problem[15,16]. CTAP, which identifies 96 per cent of lesions confirmed by histology[17], is the best method currently available. Combination with MRI has the potential to do better[18]. Despite the improved detection rate with CTAP or MRI, the incidence of recurrent hepatic nodules (40 per cent) during follow-up is evidence that micrometastases remain undetected in some patients.

The authors' policy of offering surgery to patients in whom all nodules were removable despite number and distribution has been vindicated. Survival was not affected by the number of metastases removed, confirming the work of others[7,11-13,19,20]. This does not imply that all patients with multiple metastases are operable. The policy with patients who have more than three nodules that are potentially resectable is to repeat CT after 3 months. This trial by time[21,22] selects patients with more favourable disease. Patients are offered surgery if the number of metastases remains unchanged even if they increase in size. The role of surgery for bilateral metastases is less clear but, if carefully selected, bilobar distribution should not be a contraindication to surgery[7].

In this series, there was no significant difference in survival between patients with Dukes A, B or C tumours, as found by others[10,13,19,23,24]. In contrast, other surgeons have demonstrated an improved outcome in node-negative patients[7,9,11,12,20,25,26]. In common with others, this study found that differentiation of the primary tumour did not affect survival following liver resection[13,19]. However, the number of patients with poorly differentiated tumours that were resected is small which may mask any difference in survival. The Erlangen group has recently demonstrated decreased crude survival in patients with poorly differentiated tumours[7], having previously reported no effect of grade of tumour[12].

An important finding in this study is that survival was related to size of hepatic metastases. The size of some tumours makes it difficult to obtain a clear margin especially when the metastasis is close to the efferent veins or portal structures. The advantage demonstrated for patients who have a radical resection with a margin greater than 5 mm probably reflects the easier task of achieving such margins in patients with smaller metastases. It was expected that patients with a large solitary metastasis discovered years after primary bowel surgery would have the best survival rate. This was not the case possibly because of a lead time bias in favour of smaller lumps. Large tumour deposits may not necessarily lie dormant but could possess the capacity to re-metastasize[7,27]. In eight patients tumour emboli were found within veins or portal structures in the resected specimen. In this way further spread, both local or systemic, is possible.

The results of this and other studies[7,28,29] demonstrate that hepatic resection for colorectal secondaries is justified. While the search continues for other modalities which could alter favourably the biology of the underlying tumour, surgery remains the one treatment which can produce long disease-free survival in carefully selected patients.

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Gastric emptying in patients with constipation following childbirth and due to idiopathic slow transit

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Background Idiopathic slow transit constipation (ISTC) is considered to be a heterogeneous condition in which patients have varying sites and degrees of delayed gastrointestinal transit. The majority of patients have pancolonic disease, and colectomy with ileocolorectal anastomosis has been the mainstay of surgical treatment. Severe constipation following traumatic childbirth is now being recognized and this subgroup of patients may have delayed transit confined to the rectosigmoid colon. In theory, proximal transit in these patients should be normal.

Methods Gastric emptying was studied in patients with constipation following childbirth or ISTC and in controls. After an overnight fast, both patients and controls received breakfast, which consisted of cornflakes, sugar and milk. The liquid marker ^{111}In-labelled di-ethylene tri-amine penta-acetic acid (DTPA) was added to the milk. A solid marker, ^{99m}Tc-labelled colloid, was impregnated on to paper and sealed with cellulose. The $t_{1/2}$ for gastric emptying was calculated.

Results Liquid phase emptying was normal in both constipation following childbirth and ISTC. Solid phase emptying was delayed significantly in ISTC compared with that in patients with constipation following childbirth and controls. In addition, half the patients with ISTC had delayed transit through the small bowel and proximal colon. Small bowel and colonic transit were normal in patients with constipation following childbirth.

Conclusion Patients with constipation following childbirth represent a distinct subgroup with normal proximal gastrointestinal function. Gastric emptying studies may be helpful in selecting patients for surgical management of severe constipation.

The majority of patients with idiopathic slow transit constipation (ISTC) have pancolonic disease[1,2]. The results of surgery (colectomy and ileorectal anastomosis) are variable[3–5] and may be due to proximal gastrointestinal dysmotility forming the major component of the presenting symptoms. By contrast, not all patients have pancolonic disease[6,7] and segmental colonic resection may be all that is required to return transit to normal. Hysterectomy has already been identified as a cause of regional colonic dysmotility[8], although many of its features closely resemble those of ISTC[9]. Recently, difficult childbirth has been proposed as another cause of hindgut dysmotility which might be treatable by limited resection of the rectosigmoid colon. In theory, patients who attribute their severe constipation to difficult childbirth should have normal proximal gastrointestinal transit. This study examined proximal gastrointestinal motility in patients with ISTC and constipation following childbirth.

Patients and methods

Patients with constipation following childbirth ($n = 10$, mean(s.d.) age 35(8) years), idiopathic constipation ($n = 10$, mean(s.d.) age 32(14) years) and controls ($n = 12$, mean(s.d.) age 29(12) years) were studied.

Patients were selected on the basis of their clinical history and failure to evacuate the colon of 80 per cent of radiological markers by 5 days after ingestion. The duration of symptoms ranged from 6 months to 8 years. All patients had been on long-term laxatives and/or bulking agents, without effect. None of the patients moved their bowels without the use of enemas. Stool frequency was one motion every 10–22 days. Patients and controls who had undergone previous abdominal or pelvic surgery or who had a history of peptic ulcer were excluded. Both patients and controls were asked to refrain from consuming foodstuffs or medicines that might artificially promote or delay gastric emptying for 4 days before and during the study.

Patients who attributed their constipation symptoms to childbirth had previously had normal bowel function and had not needed to take laxatives or bulking agents. Their symptoms of constipation commenced immediately after childbirth. All ten patients had had epidural analgesia for the labour and all had had a second stage of labour exceeding 2 h, eventually requiring assisted delivery (three ventouse, seven Keller's forceps). Patients with ISTC developed symptoms in their late teens or early twenties without a predisposing event. Anorectal manometry and evacuation proctography were normal in both patient groups. Controls were all women with normal bowel function (stool frequency of at least one motion every 3 days but fewer than three motions per day). Five of the 12 controls were parous but there was no history of obstetric trauma. Anorectal manometry and evacuation proctography were not performed on controls.

After an overnight fast, both patients and controls received a labelled breakfast, which consisted of cornflakes, sugar and milk. The liquid marker ^{111}In-labelled di-ethylene tri-amine penta-acetic acid (DTPA) was added to the milk. A solid marker, ^{99m}Tc-labelled colloid, was impregnated on to paper and sealed with cellulose. It was added to the cornflakes as approximately 40 small pieces of paper. Some 8 MBq indium and 80 mBq technetium were used and screening was performed using an IGE gap 400A ring-mounted γ camera (General Electric Company, Milwaukee, USA) with a medium energy collimator.

An area of interest was drawn round the stomach to monitor the rate of gastric emptying. A radionuclide marker was placed on the anterior superior iliac spine as a landmark for ileal emptying into the right colon. Anterior and posterior views of the stomach were taken, with the patient standing, every 15 min for a minimum of 2 h. Subsequent views were taken at 6, 24 and 36 h. Imaging started immediately after the labelled breakfast. Screening for the ^{99m}Tc solid phase and ^{111}In-labelled DTPA liquid phase was performed simultaneously. The geometric mean

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of the corresponding anterior and posterior images was then calculated for both the solid and liquid phases of the meal. The ^{99m}Tc channel photopeak was set at 140 KeV ± 10 per cent window The ^{111}In-labelled DTPA photopeak was set at 245 KeV ± 10 per cent. The effective dose equivalent was 5 mSv.

Results were expressed as mean(s.d.) and compared with analysis of variance (ANOVA); $P<0{\cdot}01$ was considered significant.

Approval for the study was granted by the ethics committee of Greater Glasgow Health Board. Permission to administer the isotopes was given by the Administration of Radioactive Substances Advisory Committee.

Results

The results of the gastric emptying study are shown in *Figs 1* and *2*.

Liquid phase emptying was normal in patients with ISTC and constipation following childbirth ($t_{1/2}$ 43(10) and 38(9) min respectively *versus* 42(17) min in controls; $P<0{\cdot}6$, ANOVA). Solid phase gastric emptying was profoundly delayed in patients with ISTC ($t_{1/2}$ 144(31) min *versus* 89(22) min in controls and 83(24) min in patients with constipation following childbirth, $P<0{\cdot}006$). Subsequent scanning identified the ^{99m}Tc radioisotope head in the caecum in nine of twelve controls, in nine of ten patients with constipation following childbirth, but in only one of ten patients with ISTC at 6 h. At 24 h the isotope had reached the transverse colon in nine controls, in eight patients with constipation following childbirth and in no patient with ISTC. In the latter group isotope remained in the small bowel in five cases. At 30 h the radioisotope had reached the descending colon in eight controls, eight patients with constipation following childbirth and no patient with ISTC. It persisted in the small bowel in five cases and in the ascending colon in five cases in the latter group.

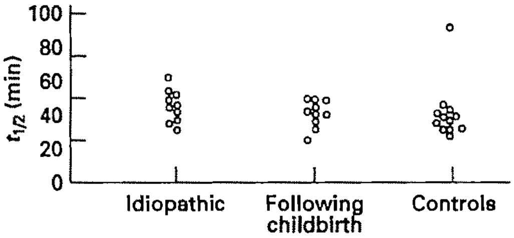

Fig. 1 Liquid phase gastric emptying in patients with idiopathic slow transit, constipation following childbirth and controls. $t_{1/2}$, time taken for 50 per cent of radionuclide to empty from stomach

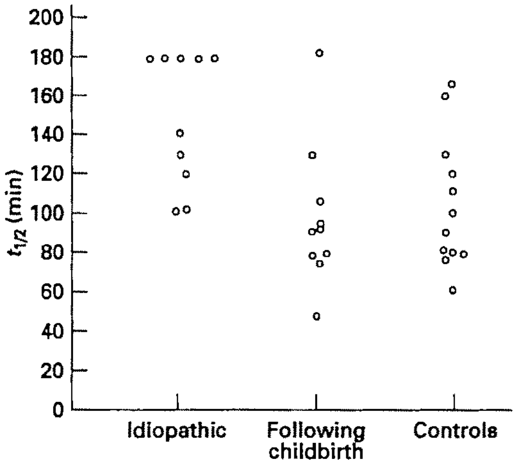

Fig. 2 Solid phase gastric emptying in patients with idiopathic slow transit, constipation following childbirth and controls. $t_{1/2}$, time taken for 50 per cent of radionuclide to empty from stomach

Discussion

The results of this study support the hypothesis that a proportion of patients with severe idiopathic constipation have, in addition, delayed transit through the proximal gastrointestinal tract[10–12]. While there is some overlap between the results from patients with constipation following childbirth, ISTC and controls, patients with constipation following childbirth clearly have normal proximal gastrointestinal transit and transit through the proximal colon. As such, hindgut dysmotility resulting from difficult childbirth appears to represent a clinical entity that is distinguishable from other types of severe constipation[1,2,11,12].

The delayed gastric emptying identified in ISTC probably reflects proximal dysmotility and is unlikely to be secondary to colonic delay in these patients. However, deliberately suppressed defaecation can inhibit gastric emptying in an experimental setting[13]. Whether or not delayed gastric emptying would revert to normal following colectomy for ISTC is not known.

Identification of normal proximal gastrointestinal transit in patients with constipation following childbirth may predict a favourable outcome from surgery (segmental colonic resection). In contrast, the profound delay identified in some patients with ISTC suggests that a major component of their presenting symptoms is related to proximal gastrointestinal dysmotility and is unlikely to be improved by resection of the colon. Although the numbers in this study are small, this observation raises the possibility that idiopathic constipation is composed of at least two pathologies: in the first, the abnormality is predominantly in the colon and patients have normal gastric emptying and small bowel transit; in the second, dysmotility is pangastrointestinal, resulting in delayed gastric emptying and prolonged small bowel transit. More patients need to be studied to confirm this initial impression.

Measurement of gastric emptying is a simple, safe and well tolerated test which can be used to identify patients with constipation who have normal proximal gastrointestinal transit. The technetium component of the meal can be followed over the subsequent 30 h to give a crude measure of small bowel and colonic transit. More importantly, the test may identify a group of patients with profound dysmotility of the proximal gastrointestinal tract in whom the results of conventional surgery are less certain.

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Comparison of computed tomography and ultrasonographic imaging in the assessment of blunt abdominal trauma in children

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Background Computed tomography (CT) has become established in the assessment of paediatric blunt abdominal trauma. However, advances in diagnostic imaging necessitate reassessment of the role of available diagnostic modalities.

Methods Experience at a paediatric teaching hospital over a 5-year period was reviewed, with direct comparison of CT against ultrasonographic imaging in 26 children presenting with acute blunt abdominal trauma.

Results Intra-abdominal injury was diagnosed by CT in 23 of 24 patients compared with 21 on ultrasonography, although ultrasonography identified organ-specific injury in only 12 of 24 patients. CT was superior in the assessment of the multiply injured child. and identified spinal and pelvic injuries in three patients. CT augmented plain chest radiography in ten patients with associated thoracic injuries.

Conclusion CT is the imaging modality of choice in children with severe abdominal trauma but ultrasonography is a reasonable technique to arouse diagnostic suspicion in less severe injuries or where CT is unavailable or delayed.

Paediatric abdominal trauma is blunt in over 90 per cent of cases with a predominant pattern of solid organ injury[1]. Most cases resolve spontaneously[2–4]. Unnecessary operation carries high morbidity[5,6], so non-operative management strategies have evolved. Accurate diagnosis of the underlying injury is therefore important to guide management decisions.

Advanced Trauma Life Support (ATLS) guidelines[7] define the role of diagnostic peritoneal lavage in the assessment of intra-abdominal trauma in adults. This technique has significant drawbacks in children[8] and makes interpretation of follow-up imaging difficult. Computed tomography (CT) has been advocated as the investigation of choice in haemodynamically stable children with severe intra-abdominal trauma[9–12]. However, ultrasonographic imaging is still widely used in the initial assessment of paediatric abdominal trauma in the UK, and is seeing a resurgence in several centres in North America[13–16]. There are no recent direct comparisons of ultrasonographic imaging with CT for abdominal trauma in children. The significance of advances in both imaging methods remains unknown and their respective roles in the current management of paediatric abdominal trauma in the UK need to be redefined.

Patients and methods

A retrospective case note review was carried out on all children admitted with blunt abdominal trauma to this hospital between March 1990 and May 1995, who had both ultrasonographic imaging and CT within 48 h of injury. Demographic details in conjunction with timing, mechanism and type of injury were recorded together with subsequent management and outcome. All radiology reports pertaining to the incident have been detailed with retrospective review of the relevant plain radiographs, and ultrasonographic and CT scans

Patients were managed initially according to standard ATLS guidelines and all were stabilized before radiological assessment. Abdominal radiology was carried out by one of four consultant paediatric radiologists. Abdominal ultrasonographic imaging was done with an Acuson 128 XP10 scanner (Acuson, Mountain View, California, USA) using a high-resolution, two-dimensional grey scale, supplemented by colour Doppler imaging. A third-generation GE Sytec (General Electric, USA) scanner was employed for CT, using both oral contrast (3 per cent non-ionic, 5–10 ml/kg) and intravenous contrast (non-ionic, 2 ml/kg). Contiguous axial 10-mm slices were made from lower thorax to pubic symphysis.

Results

Twenty-six children (20 boys, six girls) had CT and ultrasonographic imaging within 48 h of blunt abdominal trauma. These included children with clinically significant abdominal trauma who were thought to require CT and reflects a selective scanning policy directed towards severe abdominal trauma.

Median age at presentation was 7 years 7 months (range 21 months to 13 years). Mechanism of injury involved a fall in 12 cases, a road traffic accident in six (three pedestrian), bicycle handlebar injury in four, collision in two, crush injury in one and a kick to the abdomen in one patient. Nineteen injuries occurred in isolation; the other seven occurred in association with head injury (two patients), significant thoracic trauma (seven), pelvic fracture (three), spinal fracture (one) and limb fractures (two).

Significant intra-abdominal trauma was identified by CT in 22 of 26 patients, with a further suspected injury and one missed injury (*Table 1*). In two patients no severe injury was identified. Ultrasonography clearly demonstrated the organ-specific injury in 12 patients and suggested significant 'non-specific' injury in a further nine. The underlying injuries were missed in three children.

Ultrasonographic imaging demonstrated haemoperitoneum in 18 of the 21 cases detected by CT, but was less sensitive in diagnosing liver (seven *versus* 11) and splenic (seven *versus* 13) injuries (*Table 2*). Ultrasonography was slightly inferior to CT in diagnosis

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Table 1 Findings on diagnostic imaging

	Definite injury	Suspected injury	Missed injury	No injury	Total scans
Ultrasonographic imaging	12	9	3	2	26
Computed tomography	22	1	1	2	26

Table 2 Trauma identified by computed tomography and ultrasonography

	Computed tomography	Ultrasonographic imaging
Splenic injury	13	7
Liver injury	11	7
Renal injury	5	4
Pancreatic injury	0	1
Haemoperitoneum	21	18
Intestinal injury	1	0
Intrathoracic injury	10	—
Other abnormalities	6	2

of renal trauma (four *versus* five). Ultrasonographic imaging identified a case of traumatic pancreatitis which was missed on CT, but confirmed biochemically and by subsequent development of a pseudocyst. Ultrasonography, however, failed to detect a liver fracture in the same patient which was identified on CT. CT identified ten intrathoracic injuries, including pulmonary contusion (three), pleural effusion (two) and combined pulmonary contusions with effusion (five), of which only four were diagnosed by plain chest radiography. Ultrasonography is not useful for pulmonary trauma and did not identify these injuries. CT also identified six other associated injuries not seen on ultrasonography, comprising pelvic fractures (two), fractured scapula (one), fractured D7 vertebra (one), inferior vena caval dilatation (one) and intravesical blood (one).

Periportal low-attenuation zones were noted on 17 of the 26 CT examinations and were associated with liver trauma in eight patients. In nine patients this was the only abnormal liver finding; however, all of these patients had significant intra-abdominal trauma including fractured spleen (six), renal injury (two) and shattered pelvis (one). Two of these injuries occurred in association with significant pulmonary contusion and pleural effusion.

There were no deaths in this series. Twenty-two patients made an uncomplicated recovery. Two children required surgery: one needed two-stage urethral reconstruction and the other had a right heminephrectomy followed by right nephrectomy for uncontrolled bleeding. Two children had protracted morbidity. One developed a non-functioning right kidney, an injury missed on initial ultrasonography but detected on contrast-enhanced CT, and one a pancreatic pseudocyst which resolved spontaneously.

Discussion

Blunt abdominal trauma in childhood remains a significant cause of morbidity and death in children despite advances in preventive measures and intensive care. As the natural history of paediatric abdominal trauma differs from that in adults, and aggressive surgical intervention carries potentially greater morbidity, management has evolved along conservative lines[2-4,8]. The role of any diagnostic modality is not primarily to determine the need for laparotomy, but to serve as a tool on which to base subsequent clinical management, including intensity of care, level of monitoring, length of restriction in activities and guide to follow-up[17].

CT has become the imaging technique of choice in the assessment of paediatric abdominal trauma[18]. Full validation of its diagnostic accuracy remains difficult because most children do not need surgery. Previous comparisons with ultrasonography have lacked adequate methodology and contain selection bias. Advances in imaging resolution have evolved in both techniques[19].

In the present study, organ-specific injury was diagnosed on CT in 22 of 24 patients and suggested in another, yielding an accuracy comparable with that in other published series[9,11,12]. Ultrasonography was less sensitive in diagnosing solid organ injury (12 of 24) but suggested an injury in a further nine patients. Overall sonographic accuracy accords with that in previously published studies (69–94 per cent)[20]. Notably, ultrasonography missed three of 24 injuries compared with one missed by CT. It is recognized, however, that serial ultrasonographic scanning increases diagnostic accuracy.

Ultrasonography compared reasonably with CT in detection of free peritoneal fluid (18 *versus* 21 cases) but was less good at discerning liver (seven *versus* 11) and splenic (seven *versus* 13) injuries. Greater diagnostic accuracy was attained for renal trauma (four of five), although notably colour Doppler imaging failed to detect renal artery thrombosis in a child who ultimately developed a non-functioning kidney. Despite this, the ability of Doppler ultrasonography to assess vascular complications has been one of the major advances in sonographic imaging[13].

It is generally agreed that CT is superior to ultrasonographic imaging in the detection of hollow viscus and pancreatic injuries[14,21], which potentially require surgery. In this study, CT diagnosed the only case of intestinal trauma, although surgical intervention was not required. CT missed a case of traumatic pancreatitis which was detected on ultrasonographic imaging, a previously reported problem when CT is performed within 24 h, before the development of radiological change[22]. A further limitation of ultrasonography is failure to assess associated bony injuries of the spine and pelvis, which occur in approximately 10 per cent of patients[19].

Assessment of thoracic trauma is an additional advantage of CT. Chest trauma was diagnosed in ten of 26 CT studies, which compares favourably with plain chest radiography, which identified significant trauma in only four. Although this did not influence surgical intervention, improved diagnosis of thoracic trauma may guide subsequent conservative management.

Identification of low-attenuation zones surrounding the intrahepatic portal vein by CT has been linked with severe injury and risk of death. This finding has been reported previously in 15 per cent of CT scans following blunt abdominal trauma[23]. Periportal low attenuation was seen in 17 of 26 patients in this series, reflecting the policy of selective scanning for severe trauma. All of these patients had significant underlying trauma, although the liver was involved in only half.

CT was superior to ultrasonographic imaging in defining organ-specific injuries following paediatric blunt abdominal trauma. Ultrasonography was, however, capable of diagnosing significant injuries in most cases, although it remains operator dependent. The false-negative rate for ultrasonography could become significant with greater patient numbers. CT of the lower chest augments the sensitivity of radiography and, in combination with improved assessment of severity of injury, should guide the intensity of post-trauma care.

CT is the investigation of choice in children with severe blunt abdominal trauma, particularly when associated chest or bony injuries are suspected. Ultrasonography can be used to arouse diagnostic suspicion if CT is likely to be delayed or is unavailable, and may be more appropriate for less severe injuries.

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Comparison of magnetic resonance imaging and conventional triple assessment in locally recurrent breast cancer

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Background Magnetic resonance imaging (MRI) was compared with triple assessment (clinical examination, cytology and mammography) in the differentiation of post-treatment changes from local recurrence of breast carcinoma.

Methods Thirty patients treated previously by breast conservation surgery and radiotherapy with clinical suspicion of local recurrence were evaluated prospectively by triple assessment and MRI. Breast MRI was performed on a 1-tesla scanner using a T1-weighted three-dimensional fast low angle shot pulse sequence before and after contrast enhancement.

Results Local recurrence was confirmed histologically in 14 patients. Of these, mammography identified seven (sensitivity 50 per cent), cytology 11 (sensitivity 79 per cent) and breast MRI 13 (sensitivity 93 per cent). Compared with histological measurement, breast MRI allowed an accurate estimation of the extent of local recurrence ($r^2 = 0·98$). Morphologically abnormal areas without contrast enhancement correlated with postradiation changes. False-positive contrast enhancement was seen in two patients (specificity 88 per cent) in whom histology confirmed inflammatory changes only.

Conclusion Breast MRI is useful in the evaluation of patients with a high clinical suspicion of local recurrence within the irradiated conserved breast.

The optimal surveillance method for the early detection of local recurrence following breast conservation treatment remains controversial. Early local recurrence is due to residual disease and may be associated with both decreased distant disease-free survival and overall survival[1]. Patients who develop local recurrence may be treated by further surgery with approximately 65 per cent remaining disease-free at 5 years[2].

The differentiation of recurrent cancer from benign changes attributable to surgical excision and radiation treatment has been a dilemma both on clinical examination and mammography[3,4]. Post-treatment changes are non-specific and may mimic or obscure recurrent tumour[5]. Diagnostic problems are also encountered with ultrasonography because of hypoechoic areas and shadowing within scar tissue[6]. Surgical biopsy based on the results of clinical and mammographic assessment alone have a poor positive predictive value of approximately 50 per cent[7,8]. Biopsy wounds are prone to postoperative complications as healing of the irradiated breast is suboptimal.

Previous studies with contrast-enhanced magnetic resonance imaging (MRI) have shown promising results in the distinction between benign post-treatment changes and recurrent tumour However, most reports are small and include only patients with histologically proven recurrence[9–15].

The aims of this study were to compare breast MRI and triple assessment, in both the diagnosis and the extent of local tumour recurrence, in patients with a high clinical suspicion of local recurrence following breast conservation surgery, and to define the magnetic resonance enhancement and morphological characteristics of recurrent breast cancer and postirradiation fibrosis with detailed histopathological correlation.

Patients and methods

Clinical assessment

In this institution, an average of 150 women with newly diagnosed breast cancer are seen each year and breast-conserving treatment is performed in approximately 60 per cent of cases. In an 18-month interval, 30 follow-up patients with a high clinical suspicion for local recurrence within the treated breast were seen and included in the present study. These were defined as patients with a clinically palpable lump ($n = 6$) or with localized or diffuse thickening within the treated breast ($n = 24$). All except one patient had previously had breast conservation surgery with postoperative radiotherapy. The median interval from original surgery to suspected local recurrence was 52 (range 6–185) months.

Cytology

Initial assessment of the clinically suspicious region included fine-needle aspiration cytology (FNAC). Malignant cells were detected in 11, suspicious but probably benign cells in three and benign ductal cells only in the remaining 16 patients. Further outpatient histological evaluation was performed by means of needle core (Tru-cut, Travenol Laboratories, Thetford, UK) biopsy under ultrasonographic guidance in nine patients.

Mammography

Bilateral craniocaudal and oblique mammograms were performed in all 30 patients and compared with previous mammograms. Additional views were taken when necessary. The following features were recorded: number, site, size (maximum diameter) of the suspicious mass and presence of micro-

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calcifications (type, site and extent) in comparison with previous mammograms The clinical site of suspected recurrence was indicated on the request form and all mammograms were assessed by one radiologist (K.W.) experienced in mammography.

Magnetic resonance imaging

MRI was performed using a dedicated receive-only double breast coil on a 1-tesla scanner (Magneton 42SP, Siemens, Erlangen, Germany) A transverse T1-weighted three-dimensional fast low angle shot (FLASH) sequence (repetition time (TR) 18 ms, echo time (TE) 7 ms, flip angle (FA) 40°, 128 × 256 matrix, 64 partitions, effective slice thickness 2 mm, rectangular field of view (FOV) 410 mm, acquisition time 4·57 min) was made before and after enhancement with gadolinium diethylenetriamine penta-acetic acid (Magnevist, Schering, Burgess Hill, UK) at a dose of 0 1 mmol per kg body-weight. Short tau inversion recovery (STIR) sequences (inversion time (TI) 140 ms, TR 2660 ms, TE 30 ms, FA 140°, 160 × 252 matrix, effective slice thickness 5 mm, slice gap 50 per cent, acquisition time 7 min) were obtained in all patients before injection of contrast.

All breast magnetic resonance images were assessed prospectively by one radiologist (M.A.H -C.) with knowledge only of the study protocol. Abnormal masses within the breast and their enhancement characteristics were noted. The presence of focal enhancement (defined as an enhancing mass with an edge) and diffuse patchy enhancement (defined as areas of enhancement of more than 3 mm with no specific boundary to indicate a focal mass) was recorded. The number, site and size (maximum transverse diameter) of the focally enhancing areas were noted The extent of diffuse patchy enhancement was also measured, and skin and breast parenchymal changes were recorded.

Suspected recurrent cancers were classified as unifocal or multifocal (if two or more clearly separate, suspicious, enhancing lesions were seen or if there was diffuse patchy enhancement in more than one breast quadrant).

Histopathological assessment

Specimen resection margins were marked with indian ink Wide local excision and mastectomy specimens were sliced in the transverse plane at 1-cm intervals corresponding to the transverse plane of the MRI, then pinned to a corkboard and fixed in 10 per cent formalin solution. They were examined for macroscopic disease and photographed to allow comparison with the magnetic resonance images Blocks were taken from the tumour margins, nipple and retroareolar regions. Further blocks were taken from areas of interest indicated by review of magnetic resonance images. Microscopic features including tumour size (maximum transverse diameter), type, grade, presence of tumour necrosis and associated ductal carcinoma *in situ* were recorded.

Results

Table 1 summarizes the results of the study. Local recurrence was confirmed histologically in 14 patients with a median age of 52 (range 34–80) years. FNAC of the clinically suspicious region was diagnostic in 11 of these 14 patients. Presurgical diagnosis in the remaining three patients was obtained by ultrasonographically guided Trucut biopsy in two and surgical excision in one patient, in whom ultrasonographically guided biopsy was not diagnostic. Definitive surgical treatment comprised wide local re-excision in six patients and mastectomy in eight. Patients offered further breast conservation surgery had initially undergone local surgery (lumpectomy) before wide local excision or quadrantectomy as primary treatment had become policy in this unit. Axillary node clearance was performed in six patients in whom the axilla had not previously been cleared.

Table 1 Outcome of investigations in 30 patients with suspected local recurrence of breast cancer

	FNAC	Mammography	Breast MRI
No. of patients			
True positive	11	7	13
True negative	16	12	14
False positive	0	4	2
False negative	3	7	1
Sensitivity (%)	79	50	93
Specificity (%)	100	75	88

FNAC, fine-needle aspiration cytology; MRI, magnetic resonance imaging

Recurrent tumours were localized to the previously treated breast quadrant in all except one patient. The histological types of recurrent tumour were infiltrating ductal carcinoma ($n = 11$), invasive mucinous carcinoma ($n = 1$), intracystic papillary carcinoma ($n = 1$) and ductal carcinoma *in situ* ($n = 1$). The recurrent tumour was unifocal in ten, multifocal in one and diffuse in three patients. Diffuse recurrence was evident on microscopic examination as scattered cancer cells present within a fibrotic stroma. Within two of the three diffuse recurrences, a single tumour focus measuring 9 and 10 mm in diameter was seen. Diffuse recurrent tumour was localized to a single quadrant in one patient and to two quadrants in two. The median size of recurrent tumour within the conserved breast was 20 (range 8–35) mm.

Mammography identified seven of the 14 histologically proven recurrent tumours in the conserved breast. Serial mammographic examination showed that the area of abnormality was present 12 months before diagnosis in two of the seven patients, but had earlier been interpreted as suggestive of postoperative scar tissue rather than recurrent tumour. The mammographic appearance of the recurrent tumours was a spiculated mass ($n = 4$) and new microcalcifications ($n = 3$). The mammographic finding in the single patient with ductal carcinoma *in situ* was microcalcifications only. The median recorded tumour size was 13 (range 10–35) mm. Mammography underestimated tumour size in three of these seven patients. Mammographic findings in the seven patients in whom recurrent tumour was missed included deformed, dense breast ($n = 4$), scarring and benign linear microcalcifications ($n = 3$). Two of the false-negative mammograms were technically inadequate; adequate views of tumour recurrence in the axillary tail region were precluded by the firm, fibrosed nature of the breast. The sensitivity and specificity of mammographic findings for the presence of local recurrence in the conserved breast was 50 and 75 per cent respectively.

Breast MRI identified 13 of the 14 recurrent tumours. Precontrast T1-weighted images and STIR images were not on their own diagnostic of recurrent tumour (*Fig. 1a*). On the postcontrast images recurrent tumour was seen as an enhancing region of a high signal intensity compared with the adjacent irradiated breast tissue (*Fig. 1b*). Of the 13 recurrent tumours identified by MRI, seven demonstrated homogeneous enhancement, three inhomogeneous enhancement, two diffuse enhancement with a focally enhancing mass and one rim enhancement. In the patient with ductal carcinoma *in situ*, MRI showed an area of ill defined inhomogeneous enhancement. MRI identified both recurrent axillary tumours missed on mammography.

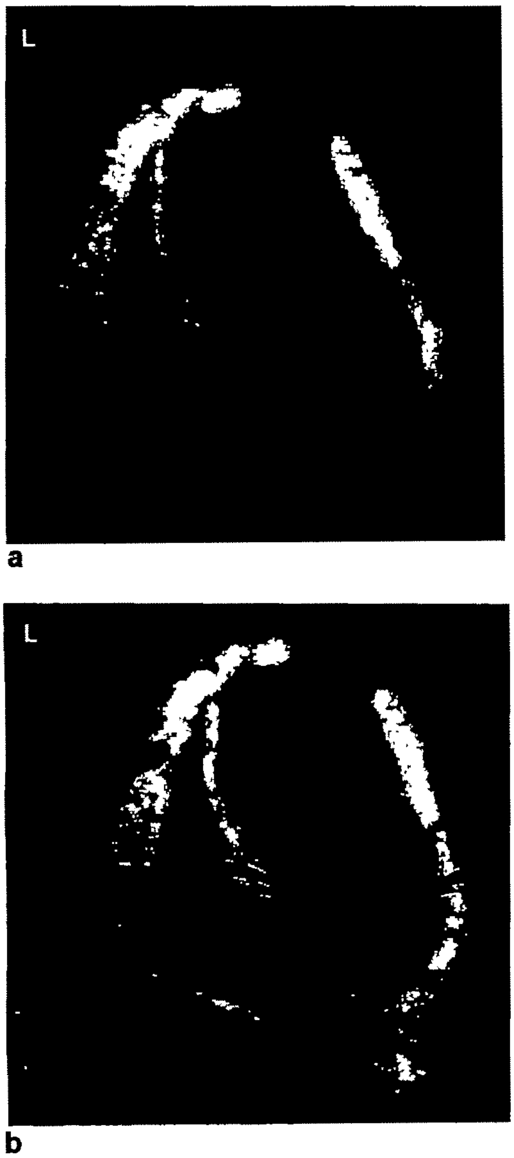

Fig. 1 Magnetic resonance imaging in a 34-year-old woman with suspected local recurrence 27 months after breast conservation surgery and adjuvant radiotherapy. a Precontrast and b postcontrast transverse T1-weighted images of the left breast show a unifocal enhancing mass (10 mm) (arrows) with background diffuse patchy enhancement mainly in the lower quadrants. Histological examination confirmed diffuse recurrent carcinoma throughout the entire breast with a single 10-mm tumour aggregate. Mammographic examination showed a dense, deformed breast but no evidence of local recurrence

The median size of recurrent tumour was 22 (range 9–35) mm, with a good correlation between the size of the unifocal cancer measured by MRI and by histopathology ($r^2 = 0\cdot98$). Magnetic resonance images identified the single tumour focus within the area of diffuse recurrence seen in two patients (*Fig. 1*). The sensitivity and specificity of MRI for local recurrence within the conserved breast were 93 and 88 per cent respectively.

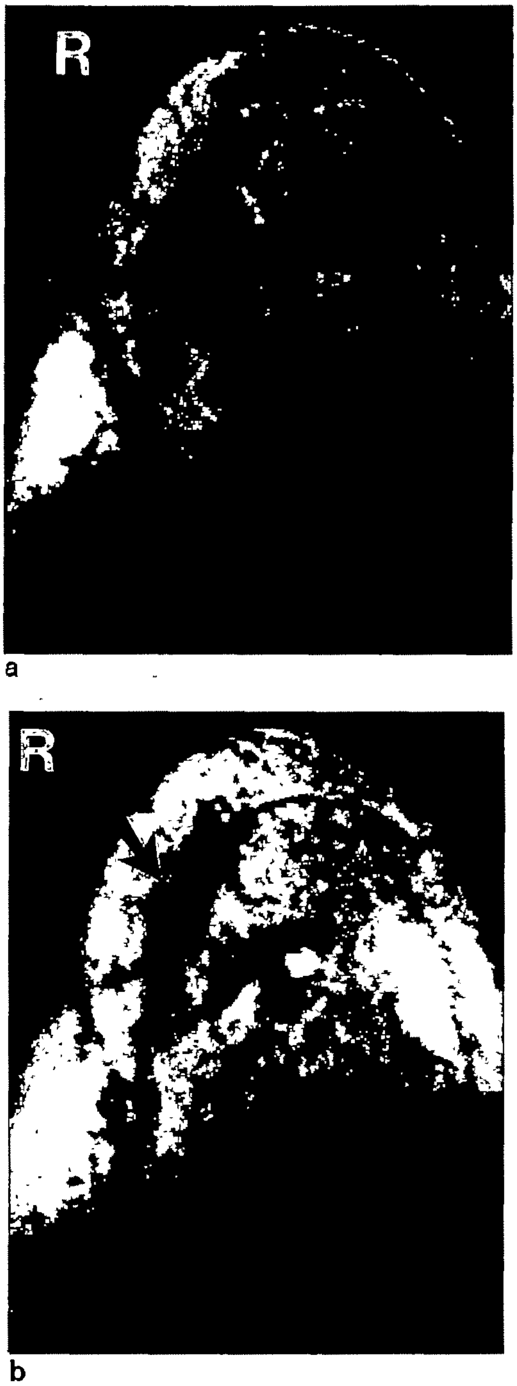

Fig. 2 Magnetic resonance imaging in a 51-year-old woman with mammographic suspicion of local recurrence at 48 months' follow-up. a Precontrast and b postcontrast transverse T1-weighted images of the right breast show an oval enhancing mass (arrow) adjacent to the site of previous surgery. Diagnostic wide local excision confirmed inflammatory changes with no evidence of local recurrence. The patient had a surgical excisional biopsy for suspected local recurrence 12 months previously

MRI failed to identify one histologically proven recurrence in a patient in whom mammography was also non-diagnostic. Clinical examination revealed a scar nodule which on cytology showed malignant cells. Histological examination showed diffuse scattered cancer cells within a dense fibrotic stroma with no discrete tumour focus.

Local recurrence was excluded in 16 patients with a median age of 62 (range 47–79) years. FNAC of the clinically suspicious region confirmed benign ductal cells in all patients. Further histological confirmation was obtained in patients with features suggestive of tumour recurrence on both mammography and MRI. This included two patients with suspicious magnetic resonance and mammographic findings, and two with suspicious mammograms only. In addition, ultrasonographically guided core biopsy was also performed in three patients with an abnormal non-enhancing mass on MRI which confirmed radiation fibrosis. In the remaining nine patients with benign cytology and with no evidence of local recurrence on mammography or MRI, further histological diagnosis was not obtained. The median follow-up for this group presently is 12 (range 6–15) months.

Contrast enhancement suggestive of tumour recurrence was seen on magnetic resonance images in two of the four patients with suspicious mammographic findings (*Fig. 2*). In view of this, a diagnostic wide local excision was performed in these two patients which showed intense areas of inflammation and postradiation fibrosis on histological examination. The interval from initial surgery in these patients was 28 and 54 months, but both previously had a surgical biopsy for possible local recurrence 12 months before MRI.

Stereotactically guided core biopsy in the other two patients confirmed postradiation fibrosis. Other benign post-treatment changes seen on MRI included linear low signal intensity non-enhancing scar ($n = 8$), skin thickening ($n = 11$) and increased signal intensity in pectoralis muscle on the STIR images ($n = 5$) due to radiotherapy damage. Post-treatment changes were evident in nearly all mammograms, including breast deformity, skin thickening, benign microcalcification and macrocalcification, and irregular scars.

Discussion

This study did not evaluate MRI as a method of serial routine follow-up of the irradiated, conserved breast but examined its possible benefits as an additional imaging technique in patients with a high clinical suspicion of local recurrence. In this unit follow-up of patients treated by breast conservation and postoperative radiotherapy includes mammography[8,16]. Clinical follow-up is conducted more frequently and has been shown in other studies to improve the detection rate of local recurrence compared with annual mammography (45 *versus* 34 per cent)[16]. Recurrences detected solely by mammography tend to be non-invasive with significantly better relapse-free and overall survival[17].

This study confirms the improved sensitivity of breast MRI in distinguishing recurrent cancer from benign postradiation and postsurgical fibrosis, findings in agreement with previous reports[9–15]. Recurrences were readily identified as enhancing lesions on T1-weighted FLASH images without the need for fat suppression or subtraction imaging. Visual subtraction of the postcontrast images allowed areas of enhancement to be identified readily in all patients in this series. This method allows the anatomical position of the areas of enhancement to be noted precisely and also reduces errors in image interpretation due to patient movement during conventional subtraction techniques. This experience with the FLASH sequence concurs with that of Heywang *et al.*[14]. The lack of contrast enhancement in morphologically abnormal areas was confirmed to correspond to post-surgical and radiation-induced fibrosis.

In this series, MRI identified an additional three patients not detected by FNAC, one of whom was not identified by ultrasonographically guided biopsy. A negative FNAC result in this clinical setting should be interpreted with caution and should not preclude further investigation of a suspect or equivocal lesion. Core needle biopsy has a higher diagnostic sensitivity and should be used to obtain a non-surgical diagnosis[18]; surgical biopsy is indicated in cases where a high index of suspicion remains.

The limited sensitivity of mammography in this series is consistent with other studies evaluating the role of mammography in the early detection of local recurrence[4,5,8,16]. In this study, mammography used as part of the triple assessment did not contribute any additional information in the diagnosis of local recurrence. Indeed, including MRI as part of the triple assessment instead of mammography would have increased the sensitivity for detecting tumour recurrence to 100 per cent.

Although serial mammography relies on changes caused by postoperative scarring to stabilize or decrease with time[4], this lack of specificity can delay early detection and treatment of local recurrence. This was observed in two of the seven recurrent tumours that were imaged repeatedly in this series. In addition, mammographic evaluation of the irradiated breast is frequently compromised by difficulty in compressing the fibrosed breast or architectural distortion or retraction. In these situations MRI is of undoubted benefit.

MRI data correlated closely with unifocal tumour size measured histologically and histopathological analysis. This may be helpful for indicating whether further conservation surgery or mastectomy is the most suitable surgical option for managing the recurrent disease. Previous studies have shown the superiority of MRI compared with mammography in the detection of multifocal recurrence[15].

False-negative MRI findings in locally recurrent tumours have not been reported previously. The single case missed by MRI in this series stresses the need for complementary clinical and cytological evaluation of all patients with suspected recurrence.

False-positive contrast enhancement seen in two patients in this series may be explained by the inflammatory changes induced by relatively recent surgical biopsies. To improve the specificity of MRI, dynamic imaging with cut-off points of peak contrast enhancement ranging from 94 s to 3 min has been suggested which will reliably differentiate recurrent tumour from postradiation fibrosis[9–11,14,15]. These studies suffer from lack of histological confirmation in over half the patients and relatively short follow-up, making an accurate assessment of the role of dynamic imaging difficult. The complex temporal changes and lesion heterogeneity observed during rapid dynamic scanning are poorly characterized by region of interest analysis which is prone to numerous errors, including the subjective choice of region shape, size and position. False-positive contrast enhancement is well reported in the literature[10,14] and occurs with both dynamic and non-dynamic MRI sequences.

Precontrast T1-weighted images on their own were not of value in diagnosis or for distinguishing between local recurrence and fibrosis. These findings are in agreement with some[9,10,15] but not all[13] recently reported studies. In addition, STIR sequences were no better at differentiating fibrosis from tumour recurrence. These observations concur with the results of Dao *et al.*[15] but differ from those reported by Weiner *et al.*[19]. High signal intensity changes in the skin and pectoralis major on the STIR sequence correlated with postirradiation changes and not tumour recurrence.

Although MRI is not recommended within 9 months of breast conservation with adjuvant radiotherapy and within 6 months of surgery alone because of false-positive contrast enhancement[12,14], it was possible to diagnose recurrent intracystic papillary carcinoma in one patient 6 months after initial surgery. However, there were two false-positive contrast enhancement results in patients who had a surgical biopsy 12 months before MRI. The authors support the reservations expressed by others[14] and caution the interpretation of images obtained within 12 months of initial surgery or radiotherapy.

This study suggests that MRI is a useful additional investigation, particularly in patients with a high clinical suspicion of local recurrence following breast conservation surgery and radiotherapy. Although the high diagnostic accuracy of MRI suggests that it may have the potential to replace conventional mammography in selected patients, this needs to be balanced against its current cost which is estimated to be 20 times more than that of mammography[20].

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Monocyte activation after open and laparoscopic surgery

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Background The level of expression of major histocompatibility complex class II antigens, human leucocyte antigen (HLA)-DR, on monocytes correlates with the development of sepsis after surgery or trauma. Normally interferon (IFN) γ can increase monocyte HLA-DR expression and thus may be a potential biological prophylactic antisepsis agent in patients suffering from accidental or surgical trauma. The purpose of this study was to determine the capacity of monocytes to respond to IFN-γ after conventional open surgery and laparoscopic surgery of similar magnitude.

Methods A whole blood flow cytometric assay was used to measure monocyte HLA-DR antigen expression before and after monocyte activation with either IFN-γ or bacterial lipopolysaccharide (LPS). Blood was obtained before operation and on postoperative day 1 from 43 patients undergoing conventional open surgery and from 15 undergoing laparoscopic surgery of similar magnitude.

Results Whole blood monocyte HLA-DR expression fell significantly after both conventional open and laparoscopic surgery. IFN-γ caused monocyte HLA-DR expression to rise by a median (interquartile range) of 43 (26–60) per cent and 63 (10–124) per cent before operation in the open and laparoscopic groups respectively. However, after operation the corresponding values were 20 (6–41) per cent and 26 (9–74) per cent ($P < 0{\cdot}003$ in all cases). Identical findings but of greater magnitude were observed with LPS stimulation before and after operation in the two surgical groups.

Conclusion Monocyte HLA-DR expression is diminished by surgical operations and is relatively refractory to further stimulation by IFN-γ or LPS after surgery. Laparoscopic surgery is as suppressive as conventional surgery in this regard. The resistance of postoperative monocytes to further activation by IFN-γ suggests that this agent may be ineffective as a biological response modifier after major surgery or trauma.

Accidental and surgical trauma are generally regarded as being immunosuppressive[1,2] and it is widely believed that this immunosuppression contributes to the aetiology of infection and sepsis after trauma and major surgical resection[3,4]. However, only very few of the individually quantifiable parameters of immunological reactivity correlate well with the development of infection and sepsis after injury[5]. The level of expression of class II major histocompatibility complex (MHC) antigens on peripheral blood mononuclear cells has consistently correlated with septic morbidity and mortality after surgery or trauma[6,7]. In one study[6] the pattern of change in monocyte MHC class II expression after accidental trauma correlated highly with clinical outcome. In that study, when an initially low level of expression rose to normal levels within 3–4 days, the clinical course was uneventful. When the rise in MHC class II expression was delayed but still occurred, the postoperative course was complicated by the development of sepsis from which the patient recovered. However, when the level of monocyte MHC class II expression failed to recover following trauma, patients frequently developed sepsis from which they died. A study conducted in patients undergoing major surgical resection of the digestive tract also revealed that the operation was associated with a large fall in the level of monocyte MHC class II expression, maximally on the first postoperative day, and that the pattern of recovery of this expression and relationship to clinical outcome was identical to that seen after non-surgical trauma[7].

These data, together with those obtained from experimental animal studies, led to the suggestion that, if the fall in the level of MHC class II expression after surgical or traumatic injury could be prevented, for example by the administration of a biological response modifier such as interferon (IFN) γ (which is a potent upregulator of MHC class II antigens on monocytes), then this might improve the clinical outcome. *In vitro* incubation of monocytes from trauma patients with recombinant IFN-γ resulted in significant upregulation of the depressed post-traumatic levels of MHC class II antigen[8]. This has resulted in clinical trials of IFN-γ as a potentially beneficial prophylactic agent in the prevention of infection and sepsis in the trauma patient[9,10]. Before such trials are considered for patients at high risk of sepsis from major elective surgery, it is important to ensure that the mononuclear cells of these patients are not refractory to the stimulatory effects of such agents. The purpose of the present study was, first, to determine whether or not the mononuclear cells of patients just after elective major surgery were responsive to a potentially therapeutic stimulant such as recombinant IFN-γ and, if not, to ascertain whether this was also the case with bacterial lipopolysaccharide (LPS), an agent that is capable of maximally upregulating MHC class II expression on monocytes and to which the cells may have been exposed at the time of the original operative procedure. To this

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end it was considered important to use a whole blood assay of monocyte MHC class II expression and stimulation rather than employing mononuclear cell isolation techniques which themselves risk monocyte activation. As it has also been suggested that immunosuppressive events evoked by conventional open surgery are attenuated when equivalent procedures are undertaken laparoscopically[11,12], the second objective was to determine whether or not the previously described suppression of basal monocyte MHC expression, which occurs after open surgery, also occurs after laparoscopic surgery.

Patients and methods

Patients

These studies were conducted in 43 patients who underwent conventional open abdominal surgery and in 15 who had laparoscopic operations. The details of these patients and operations are shown in *Table 1*. For the purpose of determining the optimum concentration of stimulants and duration of activation in whole blood, preliminary dose–concentration studies were performed on peripheral blood samples obtained from four healthy volunteer members of the laboratory staff aged between 20 and 50 years. Peripheral venous blood (4–5 ml) was collected into endotoxin-free Vacutainer tubes (Becton Dickinson, Oxford, UK) containing ethylenediamine tetra-acetic acid from each patient on the morning of operation. Because previous studies have shown that the maximum suppression of basal monocyte HLA-DR expression occurs within 24 h of injury or operation, a further blood sample was obtained from each patient at the same time on the first postoperative day.

For each sample, the percentage of monocytes was determined on whole blood films using routine haematological methods. The absolute monocyte count was then calculated from the total white cell count on each occasion.

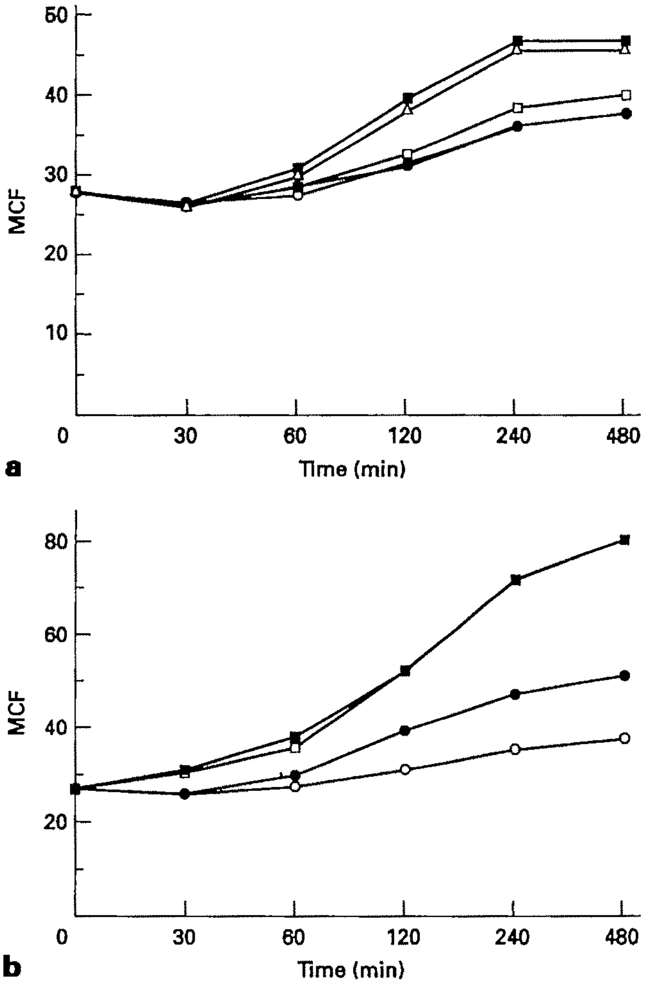

Fig. 1. Time–dose relationship between the level of monocyte human leucocyte antigen (HLA)-DR expression (expressed as mean channel fluorescence (MCF)) and the concentration of **a** interferon (IFN) γ and **b** bacterial lipopolysaccharide (LPS). ○, 0 units ml^{-1} IFN-γ and 0 ng ml^{-1} LPS; ●, 50 units ml^{-1} IFN-γ and 50 ng ml^{-1} LPS; □, 100 units ml^{-1} IFN-γ and 100 ng ml^{-1} LPS, ■ 200 units ml^{-1} IFN-γ and 200 ng ml^{-1} LPS; △, 400 units ml^{-1} IFN-γ

Sample processing

Whole blood samples from healthy volunteers were incubated at 37°C with either recombinant IFN-γ (R and D Systems, Abingdon, UK) at concentrations of 50, 100, 200 and 400 units ml^{-1} or LPS (Sigma, Dorset, UK) at concentrations of 50, 100 and 200 ng ml^{-1}, for 0, 30, 60, 120, 240 and 480 min before processing for flow cytometry as described below. Control cultures contained only an identical volume of the 'carrier' (sterile calcium- and magnesium-free phosphate-buffered saline (PBS)). Following determination of the level of monocyte HLA-DR expression, the results of these dose–response studies were plotted as shown in *Fig 1*. From these studies, the optimum concentrations and incubation times were deduced as being IFN-γ 200 units ml^{-1} for 4 h and LPS 100 ng ml^{-1} for 6 h These concentrations and times were used in the studies on patient blood samples.

Table 1 Patient characteristics

	Open surgery ($n = 43$)	Laparoscopic surgery ($n = 15$)
Mean (range) age (years)	62 (44–78)	63 (43–82)
Sex ratio (M:F)	24:19	6:9
Benign:malignant	15:28	8:7
Rectal excision	5	2
Colonic resection	12	5
Pancreatic resection	5	0
Cholecystectomy	4	4
Gastrectomy	4	0
Nissen fundoplication	1	4
Oesophagectomy	7	0
Adrenalectomy	1	0
Small bowel resection	4	0

Flow cytometry

Following incubation, 100-μl aliquots of whole blood were added to 20 μl fluorescein isothiocyanate-conjugated anti-CD14 monoclonal antibody and 2 μl phycoerythrin-conjugated monoclonal antibody against the common determinant of the HLA-DR molecule for determination of the level of expression of this MHC class II antigen on CD14-positive monocytes (All antibodies were obtained from Becton Dickinson.) Following incubation in the dark for 30 min at room temperature, the erythrocytes were lysed with Becton Dickinson lysing solution and incubated at room temperature for a further 10 min. Samples were then washed twice in calcium- and magnesium-free PBS containing 0·05 per cent sodium azide and then resuspended in 0·5 ml of the same buffer containing 1 per cent formaldehyde. The level of HLA-DR expression in these samples was determined in a flow cytometer (EPICS XL (Coulter, Luton, UK) using XL data acquisition software) by gating on monocytes which were identified by virtue of their forward light scatter and anti-CD14 staining characteristics. Mean channel fluorescence (MCF) for phycoerythrin was recorded for each sample.

Data analysis

The results were determined as the absolute MCF (in MCF units) and expressed for each group as the median MCF and interquartile range (i.q.r.) with and without activation *in vitro* before and after operation. Paired data (with and without activator, before and after operation) were compared with the Wilcoxon signed rank test. Data were also expressed as the percentage change in monocyte HLA-DR expression under the various conditions, and were also compared with the Wilcoxon signed rank test. Differences between the percentage changes in HLA-DR expression under the various conditions between the open and laparoscopic surgery groups were compared with the Mann–Whitney U test A probability of 0·05 or less was considered to be significant.

Results

Effects of surgery on the level of expression of human leucocyte DR antigen on monocytes

There was no difference between the median (i.q.r.) baseline levels of HLA-DR expression on monocytes derived from the laparoscopy (47 (44–64) MCF units) and conventional open surgery (37 (26–57) MCF units) groups before operation. In the group that underwent conventional open surgery the median basal level of monocyte HLA-DR expression fell to 20 (i.q.r. 10–29) MCF units on the first postoperative day ($Z = -4{\cdot}68$, $P = 0{\cdot}0001$) and in those undergoing laparoscopic surgery it fell to 25 (12–40) MCF units ($Z = 2{\cdot}92$, $P = 0{\cdot}004$). Similar baseline results were observed for the preoperative data from control (non-activated) samples for both the IFN-γ- and LPS-activated monocytes.

Effects of interferon-γ on monocyte human leucocyte DR antigen expression

In the patients who underwent conventional open surgery, incubation of preoperative samples of whole blood with IFN-γ 200 units ml^{-1} resulted in an increase in monocyte HLA-DR expression from a baseline of 28 (20–36) MCF units to a level of 38 (28–64) MCF units ($Z = 5{\cdot}16$, $P = 0{\cdot}0001$). On postoperative day 1, after open operation, baseline HLA-DR expression fell to a level of 12 (9–16) MCF units; incubation with IFN-γ produced a rise to a median of 15 (i.q.r. 10–23) MCF units ($Z = 3{\cdot}94$, $P = 0{\cdot}001$). However, the level of IFN-γ-induced HLA-DR expression after surgery remained significantly lower than baseline levels observed before open operation ($Z = 5{\cdot}14$, $P = 0{\cdot}0001$). In the laparoscopy group, before operation, IFN-γ produced a rise in the level of HLA-DR expression from 35 (28–47) MCF units at baseline to 60 (35–79) MCF units ($Z = 3{\cdot}41$, $P = 0{\cdot}0007$). On the first postoperative day after laparoscopic surgery baseline levels of expression had fallen to 18 (10–29) MCF units (preoperative *versus* postoperative baseline level, $Z = 2{\cdot}93$, $P = 0{\cdot}003$), and this could be increased to a median of only 28 (12–39) MCF units by incubation with IFN-γ. The level of IFN-γ-induced monocyte HLA-DR expression after laparoscopic surgery was significantly lower after operation than it was before operation ($Z = 2{\cdot}93$, $P = 0{\cdot}003$). Thus, in this component of the study, baseline levels of MHC expression fell after surgery and, although significant upregulation of monocyte HLA-DR expression could be achieved by incubation with IFN-γ, these cells were relatively refractory to this stimulus (*Fig. 2a*).

Effects of lipopolysaccharide on monocyte human leucocyte DR antigen expression (Fig. 2b)

In the group of patients undergoing conventional open surgery, before operation incubation of whole blood with LPS caused the median level of monocyte HLA-DR expression to rise significantly from 37 (i.q.r. 26–57) to 90 (58–144) MCF units ($Z = 5{\cdot}8$, $P = 0{\cdot}0001$). After operation, incubation with LPS resulted in a rise in the median level of monocyte HLA-DR expression from 20 (10–29) to 34 (17–48) MCF units, which was also statistically significant ($Z = 5{\cdot}80$, $P = 0{\cdot}001$). Nevertheless, the level of HLA-DR expression on postoperative monocytes after LPS activation still remained significantly lower than that seen after LPS stimulation before surgery ($Z = 5{\cdot}04$, $P = 0{\cdot}0001$). In the group of patients undergoing laparoscopic surgery, LPS produced a rise in HLA-DR expression from a median of 47 (i.q.r. 44–64) MCF units to 141 (94–154) MCF units ($Z = 3{\cdot}40$, $P = 0{\cdot}0007$) before surgery, and after operation caused the basal level of expression to rise from 25 (12–40) to 41 (24–65) MCF units ($Z = 3{\cdot}40$, $P = 0{\cdot}0007$). This level of expression was lower than that seen before laparoscopic surgery ($Z = 3{\cdot}41$, $P = 0{\cdot}0007$).

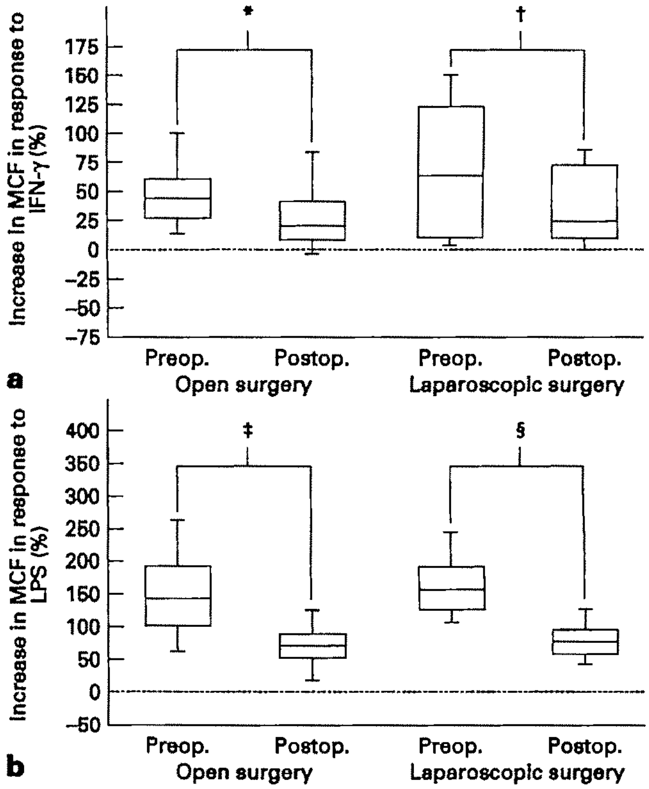

Fig. 2 Percentage increase in monocyte human leucocyte antigen (HLA)-DR expression in response to activation of whole blood with a interferon (IFN) γ and b lipopolysaccharide (LPS) *in vitro* before and after open and laparoscopic surgery. Horizontal lines represent median values, boxes are interquartile ranges and error bars represent 10th and 90th centiles. MCF, mean channel fluorescence. *$Z = 5{\cdot}14$, $P = 0{\cdot}0001$; †$Z = 2{\cdot}93$, $P = 0{\cdot}003$; ‡$Z = 0{\cdot}04$, $P = 0{\cdot}0001$; §$Z = 3{\cdot}40$, $P = 0{\cdot}0007$

Effects of surgery on whole blood monocyte count

The median (i.q.r.) percentage of monocytes present in whole blood before operation was 5·4 (4·1–7·0) per cent and 4·4 (3·2–4·4) per cent in the open and laparoscopic groups respectively. The corresponding values on postoperative day 1 were 5·1 (3·7–6·3) per cent and 5·3 (2·9–6·9) per cent. None of these values was different from any other. There were no statistically significant differences in the absolute monocyte count between the two groups.

Discussion

Class II (HLA-DR) antigens of the MHC serve a number of functions within the immune system. Amongst the most important of these is the presentation of processed antigen by accessory cells such as monocytes and macrophages to other cells such as T and B cells. Without such antigen processing and presentation, an effective immunological response cannot be generated. Theoretically, therefore, the level of expression of MHC class II antigens on monocytes and macrophages in surgical patients has a clinical influence, because failure of MHC class II antigen expression results in failure of antigen presentation. Several studies have demonstrated the profound downregulation of monocyte MHC class II expression that occurs after surgical or traumatic injury[6,7,13,14] In trauma patients this finding has been sufficiently consistent to be incorporated advantageously into a modified Injury Severity Score[15], and the level and pattern of change of MHC class II antigen expression on monocytes correlates closely with the clinical outcome after both trauma[6] and elective major surgery[7]. Moreover, based on the suggestion that MHC class II expression after traumatic injury can be amplified by monocyte exposure to activators such as IFN-γ[8], several studies of the use of IFN-γ as an adjuvant after major injury have been conducted, with results which are as yet inconclusive although a trend towards improvement in the sepsis-related mortality rates in the IFN-γ treated groups has been reported[9,10]. Although preliminary trials of macrophage-directed immunostimulants have already been reported in high-risk surgical patients[16], these have been undertaken before determining whether or not postoperative monocytes were refractory to the activating properties of agents such as IFN-γ.

The results of this investigation confirm data obtained from previous reports that the level of expression of MHC class II antigens on monocytes falls after major elective surgery[7,13]. In addition it would appear that this occurs irrespective of the severity of the surgical injury because similar degrees of reduction of monocyte MHC class II expression occur following open and laparoscopic surgery of similar magnitude. This is in contrast to previous reports in which, compared with conventional open surgery, parameters such as neutrophil function[11] and cytokine release[12] were relatively well preserved following laparoscopic surgery. In view of the suggestion that infectious complications occur less frequently after laparoscopic surgery, the relationship between these immunological changes, the magnitude of the surgical insult, and the development of postoperative sepsis may be more complex than was previously considered.

The second finding from this study is that, irrespective of the magnitude of the surgical injury (i.e. conventional open or laparoscopic surgery), the level of expression of MHC class II antigens on monocytes cannot be augmented by incubation *in vitro* with IFN-γ after operation to the same degree that it can before surgery. Furthermore, the present data suggest that the level of upregulation of monocyte HLA-DR that can be induced after operation does not appear to be as great as that reported in the original observation by Hershman *et al.*[8]. There may be technical reasons for this discrepancy. Hershman and co-workers employed isolated monocytes for their IFN-γ stimulation procedures, whereas the present studies attempted to emulate the clinical application by culturing whole blood with IFN-γ before undertaking flow cytometry. This might imply that other factors are operative in the whole blood preparations from patients after trauma which inhibit monocyte activation as determined by HLA-DR expression. Presumably such factors are also operative *in vivo*, which might explain why the clinical trials of IFN-γ in the prevention of sepsis after trauma have been less successful than anticipated.

Similar findings were observed when LPS was used as the monocyte activator in these studies. LPS is considered to mobilize intracellular stores of HLA-DR antigen[17] and thereby cause greater upregulation of surface HLA-DR expression. The cause of reduced monocyte HLA-DR expression after surgery or trauma is as yet unknown, but these findings suggest that at least part of the reason may lie in failure of mobilization of intracellular stores following maturation. Such an event is known to occur in the cell surface expression of an important immunoglobulin G receptor (CD16) on postoperative neutrophils[18]. Expression of the LPS-binding protein receptor CD14 was used in the present study as a marker for the identification of peripheral blood monocytes. All peripheral monocytes express this antigen but the authors have recently described the existence of two subpopulations of CD14-expressing monocytes in the peripheral blood, namely 'strong' and 'weak' CD14 expressers. Although in this paper changes in CD14 expression have not been commented on, there does appear to be a reduction in the numbers of circulating CD14 'weak' expresser monocytes after major abdominal surgery, suggesting that mature activated monocytes are removed from the circulation during surgical stress[19].

The whole pattern of suppression of cytokine production following surgery or trauma with failure of interleukin (IL) 2 and IFN-γ production suggests a shift from T helper 1 function to T helper 2-type activation. In humans these two types of T cell are phenotypically indistinct and can be identified only on the basis of their cytokine production patterns. IL-10 is a T helper-2-derived cytokine previously described as cytokine synthesis inhibitory factor. IL-10 inhibits the production of autoregulatory cytokines by T cells and monocytes, but activates antibody production by B cells. Administration of recombinant IL-10 results in a neutrophil leucocytosis and causes downregulation of MHC class II expression on human mononuclear cells. Recent evidence suggests that it accomplishes the latter by inhibiting the mobilization of preformed HLA-DR molecules from intracellular stores. IL-10 thus possesses many of the characteristics of an immunoregulatory cytokine which may play a role in the downregulation of monocyte HLA-DR antigen expression after surgery and trauma, and current efforts are directed at determining its role in this regard[20].

In summary, this study has revealed that, using a whole blood technique, monocyte HLA-DR expression is downregulated following elective surgical intervention irrespective of whether this is accomplished by conventional open techniques or by minimal access procedures. That these postoperative peripheral blood mononuclear cells are relatively refractory to restoration of their preoperative levels of monocyte HLA-DR antigen expression by stimulation in whole blood with agents such as IFN-γ and bacterial LPS is rather counter to current views concerning the administration of such agents as biological response modifiers against the development of infection and sepsis after surgery and trauma. Such clinical trials as have been conducted have met with varying degrees of success, possibly because monocytes are refractory to further activation as described above. This does not detract from the concept of biological response modification[21] in the prophylaxis of surgical sepsis but, rather, argues for more detailed dissection of the mechanisms underlying these sepsis-related biological phenomena so that clinical trials may be designed more logically.

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Evaluation of the antireflux mechanism following laparoscopic fundoplication

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Background Laparoscopic Nissen fundoplication is an effective procedure for the treatment of gastro-oesophageal reflux disease (GORD), but the underlying motility mechanisms that explain the success of this operation remain unclear.

Methods Twenty patients with a history of GORD underwent stationary oesophageal manometry and prolonged ambulatory pH monitoring, both before and 3 months after fundoplication.

Results Eighteen patients were completely cured of reflux symptoms and stopped all antireflux medication after operation. After fundoplication there was a significant increase ($P < 0{\cdot}01$) in median resting lower oesophageal sphincter (LOS) pressure and length. Median residual LOS pressure during swallow-induced LOS relaxation also increased significantly after operation ($P < 0{\cdot}01$). The number of reflux episodes decreased from a median of 48 to 3 after fundoplication ($P < 0{\cdot}01$). The time at pH less than 4 decreased from 5·7 to 0 per cent in the supine position ($P < 0{\cdot}01$), and from 9·8 to 0·2 per cent while upright ($P < 0{\cdot}001$).

Conclusion Early subjective results at 3 months following laparoscopic antireflux surgery show improved symptoms. One of the mechanisms underlying the antireflux action of fundoplication is an increase in median residual LOS pressure at the gastro-oesophageal junction. This may be a purely mechanical effect of the fundic wrap extrinsic to the LOS.

Gastro-oesophageal reflux disease (GORD) is the most common upper gastrointestinal disease in the Western population, producing heartburn and regurgitation in symptomatic individuals[1]. Approximately 10–15 per cent of patients develop serious complications such as ulceration, stricture and Barrett's metaplasia, even after medical therapy. Although medical therapy may control symptoms in most cases, some patients require surgical correction of the pathophysiological abnormality causing reflux.

Since the first fundoplication by Nissen[2] more than 40 years ago, an associated physiological disturbance of the lower oesophageal sphincter (LOS) has become widely accepted as a cause of gastro-oesophageal reflux[3]. The advent of minimally invasive techniques, including laparoscopic fundoplication, during the past 5 years has revolutionized the surgical management of GORD. However, there is a paucity of objective preoperative and postoperative data in reports of laparoscopic fundoplication[4–7]. This study concerns the results of laparoscopic antireflux surgery, with particular emphasis on the antireflux mechanism as assessed objectively by oesophageal manometry and prolonged ambulatory pH monitoring.

Patients and methods

Between October 1992 and June 1995, 23 patients underwent laparoscopic antireflux surgery, 20 of whom were available for preoperative and postoperative objective analysis. Three patients refused postoperative studies. There were 11 women and nine men of median age 43 (range 30–73) years. The majority of patients (14 of 20) presented with pyrosis and epigastric pain. The others presented with chronic cough in the absence of other symptoms (two patients), reflux laryngitis and vocal problems (two), chest pain (one) and respiratory symptoms with exacerbation of asthma (one). The indication for surgery was medically refractory GORD in 15 patients, concern about long-term medical therapy in three and drug intolerance in two.

Preoperative evaluation included a complete history and physical examination, prolonged ambulatory pH monitoring, stationary oesophageal manometry, oesophagogastroduodenoscopy with biopsy, and barium oesophagraphy. In selected patients, pulmonary and comprehensive voice evaluations were also performed. The patients were seen for follow-up 2 weeks after operation. All patients underwent prolonged ambulatory pH monitoring and stationary oesophageal manometry again at 3 months. Median follow-up was 18 (range 3–40) months.

Surgical procedure

Laparoscopic fundoplication was performed by one of the authors (D.M.S.), as described elsewhere[4–6]. Sixteen patients underwent a Nissen–Rosetti fundoplication, in which the short gastric vessels were not divided. In two patients, a complete Nissen fundoplication was performed. Two patients with distal aperistalsis underwent a Toupet partial fundoplication. There was one concomitant cholecystectomy and one concomitant umbilical hernia repair. The wrap was calibrated over a 54-Fr Maloney dilator and measured 2 cm in length. The crura were closed selectively.

Median operating time was 4·1 (range 2·2–6·2) h and median length of stay in the hospital was 4 (range 2–12) days. A nasogastric tube was not used routinely and all patients underwent a Gastrografin (Schering, California, USA) swallow on the first postoperative day. All patients received preoperative antibiotics and subcutaneous heparin prophylactically, as well as antithrombosis stockings. Subcutaneous heparin was continued for 48 h after operation.

Oesophageal manometry

After an overnight fast, oesophageal manometry was performed using a solid-state intraluminal transducer assembly (Konigsberg Instruments, Pasadena, California, USA). The catheter consists

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of a flexible tube containing four small pressure transducers, the distal two of which are circumferential, recording and averaging pressure over 360°. The two proximal transducers have a single sensor oriented in one direction. Pressure data were collected online by means of a computerized motility system, and analysed using Polygram equipment and software (Synectics Medical, Irving, Texas, USA).

The LOS was assessed by means of a station pull-through technique and its relaxation (residual pressure) was assessed with six 5-ml water swallows while a circumferential transducer was positioned in the high-pressure zone. Normal values for mid-respiratory LOS resting and residual pressures in the authors' laboratory are 15–45 and 8 mmHg or less respectively[8]. Oesophageal peristalsis was measured using ten wet swallows (5 ml water) with the catheter in two locations: (1) distal oesophageal function with recording of pressures at 3, 8 and 13 cm above the LOS; and (2) proximal oesophageal function with recording of pressures at 1, 6 and 11 cm below the upper oesophageal sphincter. All manometric tracings were reported according to previously defined criteria[9].

Prolonged ambulatory oesophageal pH monitoring

This was performed with a Synectics portable pH measuring unit (model 93-6200 dual-channel Digitrapper) using a monocrystalline antimony pH electrode (model 91-0215; Synectics Medical) and a silver–silver chloride electrocardiographic reference electrode, both initially calibrated in buffer solutions of pH 7 and pH 1. The pH electrode was located 5 cm above the proximal margin of the LOS, determined previously by manometry. The reference electrode was placed on the chest.

All patients were instructed to pursue normal activities. There were no meal restrictions, with the exception of avoiding food and beverages high in caffeine. Each individual was given a personal diary to note meal times (including beverages), recumbent periods, any symptoms (e.g. chest pain, heartburn), the times they occurred and the severity of each episode. Postprandial periods were defined as the 2 h immediately after the end of a meal. Data from the Digitrapper were loaded into a computer and analysed with the Synectics Esophagram program (Esophagram Software Package; Gastrosoft, Chicago, Illinois, USA), including elimination of actual meal periods from analysis. Based on previous studies[10], distal reflux was defined as abnormal if the percentage of time that the pH was below 4·0 exceeded the upper limit of normal, previously defined for the authors' laboratory for any one of the three parameters: 6·3 per cent for the upright period; 1·2 per cent for the recumbent period, and 4·2 per cent for the total period. No symptom score or scale was used.

Statistical analysis

Values were expressed as median and range. Comparison between preoperative and postoperative (paired) data was with the Wilcoxon matched-pairs signed-rank test using True Epistat (version 3·1) for IBM PC for Windows (Richardson, Irving, Texas, USA). Statistical significance was set at the 0·05 level.

Results

Eighteen patients were completely cured of reflux symptoms and were off all antireflux medications after operation. Two patients had incomplete resolution of symptoms. One of these had an open Nissen fundoplication 3 months after the laparoscopic procedure because of persistent symptoms. He is currently asymptomatic following revision surgery. In the second case, the patient presented with intractable coughing with meals. Extensive multidisciplinary evaluation revealed GORD as the only abnormality. Although her symptoms were atypical and imperfectly correlated with episodes of reflux by 24-h pH monitoring, she was offered fundoplication with the understanding that any components of the symptoms that were not due to reflux would not be improved with surgery. There was significant oesophageal dysmotility, so partial fundoplication was performed. After operation, the symptoms were partially but not completely improved. Postoperative 24-h pH study showed no pathological reflux. The patient sought a second opinion at another medical centre and underwent an open Hill repair with resolution of symptoms. One patient continued to have poorly defined abdominal pain following the procedure, although objectively there was no evidence of reflux on ambulatory pH monitoring.

Complications included asymptomatic pneumothorax (four patients) and pulmonary embolism (two). One patient contracted *Clostridium difficile* diarrhoea and another developed an incisional hernia at the camera insertion site. There were no deaths and conversion to an open procedure was not necessary in any patient.

Manometry

There was an increase in the resting LOS pressure in 11 of the 20 patients. The median (range) resting LOS pressure increased significantly ($P<0{\cdot}01$), from 26·5 (12–88) to 34·0 (16–55) mmHg after operation. There was an increase in residual LOS pressure during swallow-

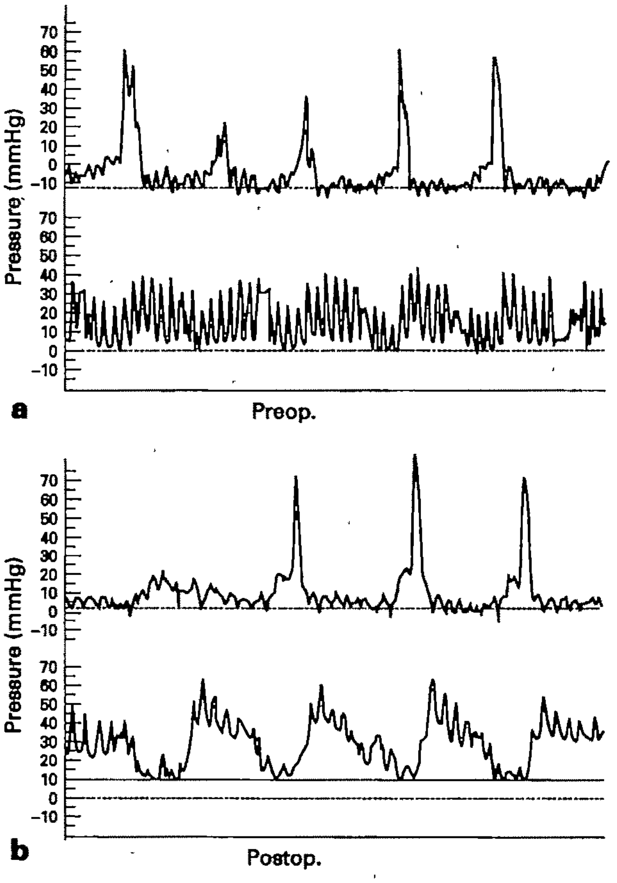

Fig. 1 Manometric tracings showing lower oesophageal sphincter (LOS) relaxation **a** before and **b** 3 months after laparoscopic fundoplication. Before fundoplication a 5-ml water swallow induced complete LOS relaxation, compared with a residual pressure of about 10 mmHg after fundoplication. ....., Gastric baseline pressure; ———, nadir of LOS relaxation

Table 1 Motility characteristics of seven patients with ineffective distal oesophageal motility

	Peristaltic contractions (%)		Distal oesophageal contraction amplitude (mmHg)		
	Preop.	Postop	Preop	Postop	Procedure
Patient no.					
1	0	10	28	105	Toupet–Hill
2	10	40	29	45	Nissen
3	10	50	93	85	Nissen
4	40	10	87	69	Nissen
5	20	10	44	45	Nissen
6	40	20	62	50	Nissen
7	0	0	28	27	Toupet
Mean	16	20	53	61	
Median	10	10	44	50	
Range	0–40	0–50	28–93	27–95	
P*		0·3		0·3	

*Postoperative *versus* preoperative value (Wilcoxon paired signed-rank test)

induced LOS relaxation in 17 patients. Following fundoplication, the median (range) residual pressure increased from 0 (0–14) to 9 (0–16) mmHg ($P<0{\cdot}01$) (*Fig. 1*).

The intra-abdominal length of the LOS (high-pressure zone), determined as the amount of sphincter below the respiratory inversion point, increased significantly ($P<0{\cdot}01$) from a median (range) of 3 (1·5–5·0) to 4 (2·5–6·0) cm after surgery. The intra-abdominal length of LOS increased significantly ($P<0{\cdot}01$) in 15 patients. The amplitude of distal oesophageal contractions was not significantly affected by the operation. Of the seven patients with ineffective oesophageal motility in the distal oesophagus, two had severe dysmotility before operation and were treated with a Toupet fundoplication. There was no significant change in peristalsis in any of these seven patients following surgery (*Table 1*).

pH monitoring

The total number of reflux episodes during the monitoring time decreased from a median (range) of 48 (2–107) to 3 (0–12) ($P<0{\cdot}01$) after fundoplication. The median (range) percentage time at pH less than 4 decreased from 5·7 (0–38) to 0 (0–6) per cent in the supine position ($P<0{\cdot}01$), and from 9·8 (0–40) to 0·2 (0–7) per cent while upright ($P<0{\cdot}001$). Improvement in the reflux parameters occurred in all 20 patients.

Discussion

Following the serendipitous discovery of the LOS manometrically by Fyke and colleagues[11], there has been a surge of enthusiasm regarding its role as the physiological deterrent to the reflux of gastric contents back into the oesophagus. Although resting LOS tone is generally considered to be the major antireflux component, the exact mechanism of reflux is a complex and multifactorial phenomenon[12]. Various anatomical factors play a pivotal role in preventing reflux, including the 'flap-valve' effect of the acute angle of His and the mucosal rosette[13], the gastric sling fibres[14], the intra-abdominal length of the oesophagus[15] and the diaphragmatic crural sling with its 'pinch-cock' action[16]. However, despite recently recognized factors such as transient relaxation of the LOS and delayed gastric emptying[17,18], the exact pathophysiological mechanism of reflux remains elusive.

Antireflux surgery is designed to correct the mechanically defective LOS, which accounts for about 70 per cent of GORD[18]. Although chronic hypotonia of the LOS[19] has been considered to be the *sine qua non* for gastro-oesophageal reflux, a recent report[20] has shown that gastro-oesophageal reflux occurs in patients with a hypertensive LOS. In the present study, none of the patients with objective evidence of reflux had a hypotensive LOS. In fact, four patients had a hypertensive LOS before surgery. After operation, their resting pressures fell, with both objective and subjective control of reflux.

Various studies have shown that open fundoplication results in a significant rise in resting LOS pressure[21–23]. Hinder *et al.*[24] demonstrated a significant increase in mean resting LOS pressure following laparoscopic Nissen fundoplication in their series of 51 patients who underwent manometric evaluation 3–12 months after operation. More recently, McAnena and colleagues[25] confirmed this increase in 12 of 15 patients treated with laparoscopic fundoplication for gastro-oesophageal reflux. The present results are consistent with these findings.

DeMeester *et al.*[22] suggested that, among the traditional surgical procedures, Nissen fundoplication achieves the best objective control of gastro-oesophageal reflux. Skinner[18] has also emphasized the importance of the intra-abdominal length of the high-pressure zone. The intra-abdominal length of the LOS was increased significantly in 15 of the present 20 patients after operation ($P<0{\cdot}01$).

In addition to low basal LOS pressure, episodes of reflux tend to occur with brief periods of sphincter relaxation, which are either swallow-induced or occur inappropriately[26]. Increased frequency of spontaneous transient relaxations of the LOS[27] seems to be another vital factor in allowing access of gastric contents to the oesophageal lumen. In a study of 18 patients who had open fundoplication, Ireland *et al.*[28] demonstrated a significant change in the ability of the LOS to relax on swallowing. They suggested that augmentation of the mean residual LOS pressure at the cardia was the major antireflux mechanism following open fundoplication. In a study of 41 patients, Kiroff and colleagues[29] showed a significant increase in the residual LOS pressure on swallowing in most of their patients after open surgery. In the present series, the median LOS residual pressure during swallow-induced LOS relaxation was significantly increased ($P < 0{\cdot}01$) in 17 of the 20 patients after surgery, corroborating the results of open fundoplication. Thus, one of the antireflux mechanisms following laparoscopic fundoplication is an increase in the residual LOS pressure and failure of complete relaxation of the LOS.

One of the factors responsible for reflux oesophagitis is the reduced ability of the oesophagus to clear refluxed acid by coordinated peristaltic contractions. The effect of successful treatment of acid reflux on oesophageal motor coordination remains controversial. In a controlled study, Russell *et al.*[30] demonstrated that the oesophageal motor dysfunction seen in some patients with reflux disease does not improve after surgical correction of reflux. Half of their patients had distal oesophageal motor dysfunction on radionuclide transit studies before surgery. The abnormality persisted consistently in all patients after surgical correction of reflux. Johnsson and colleagues[31] also found no significant improvement in the distal oesophageal contraction amplitude at manometry, 6 months after open fundoplication. Conversely, DeMeester *et al.*[22] suggested that the motility abnormalities seen in patients with GORD improve after surgical correction of reflux. In the present series, distal oesophageal dysmotility was present in one-third of patients before operation; there was no significant improvement in motor function 3 months after operation.

Prolonged ambulatory pH monitoring has emerged as the 'gold standard' for the quantitative measurement of oesophageal acid exposure. The objective goal of therapy is to reduce oesophageal exposure to gastric juice. The intraoesophageal pH profile was restored to normal in all patients after operation in the present series. The primary aim of antireflux surgery is to restore the competence of the cardio-oesophageal junction while maintaining the patient's ability to swallow normally. This goal can be accomplished if certain principles are applied in reconstructing the cardia, regardless of the surgical procedure used. The operation should restore the basal LOS pressure to at least twice that of the resting gastric pressure and should augment the overall length of the sphincter to at least 3 cm[32]. Increasing the length of the LOS exposed to the positive intra-abdominal pressure is also necessary. Fundoplication, whether open or laparoscopic, achieves this by buttressing the distal oesophagus with the stomach. The overall effect may be transmission of the gastric muscle tone to the distal oesophagus due to the fundic wrap, and also an augmentation of the length of the high-pressure zone exposed to the intra-abdominal positive pressure. This may aid in preventing reflux caused by chronic hypotonia of the LOS, gastric dilatation and inappropriate relaxation of the sphincter.

In summary, this study demonstrates that laparoscopic antireflux surgery is an effective therapeutic option in selected patients with GORD. Early results show an improvement in symptoms, altered LOS function and decreased gastro-oesophageal reflux similar to those observed after open operation.

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Short note

Spleen-sparing surgical treatment for echinococcosis of the spleen

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Hydatid disease, or echinococcosis, is a parasitic condition usually caused by *Echinococcus granulosus*. It is endemic in some Mediterranean areas, South America, South Africa, Australia and some countries of Eastern Europe. Most of the cysts (50–80 per cent) are found in the liver. Other organs involved are the lung, kidneys and spleen[1]. Hydatid disease of the spleen is very rare, even in endemic areas (0·5–4 per cent of all cases of echinococcosis)[1,2]. Until recently, splenectomy was the recommended surgical procedure. Since 1980 there has been an increasing tendency to use conservative surgical methods of treatment as splenic preservation has become desirable.

Patients and methods

From 1982 to 1994, 377 patients with hydatid disease were treated in this hospital department. The spleen was infected in only ten patients (2·7 per cent) and was the sole site of infection in two cases (0·5 per cent). Liver and spleen were affected in six patients; liver, spleen and peritoneal cavity in one; and spleen, omentum, mesocolon and diaphragm in one.

The diagnosis was confirmed with ultrasonography and computed tomography (*Fig 1*), to rule out other silent locations, as well as by estimation of antibody titre (mainly for postoperative follow-up). The standard surgical procedure for the splenic cyst was partial cystectomy with subsequent omentoplasty and drainage. The steps of the operation are: isolation of the operative field, paracentesis of the cyst at its lowest point (mobilization of the spleen should not be carried out), meticulous washing of the cavity using 0·9 per cent sodium chloride and povidone–iodine, careful haemostasis of the cyst edges, suturing of omentum on the cyst edges with 2/0 chromic catgut sutures, and finally placement of two drainage tubes, one in the residual cavity and one along the left paracolic gutter. Other coexistent cysts were treated appropriately to the location.

Results

Follow-up of all patients over a period of 1–12 years showed that obliteration of the cavity was complete and the spleen was retained successfully.

Postoperative complications included one patient with pleural effusion and one with pyrexia and hyperamylasaemia. No reoperation was needed. In the two cases where the spleen was the only location of infection, discharge from hospital was on the seventh and tenth postoperative days. In the other cases postoperative stay ranged from 8 to 31 days (delay was mainly due to bile leakage, as a complication of treating a hepatic cyst).

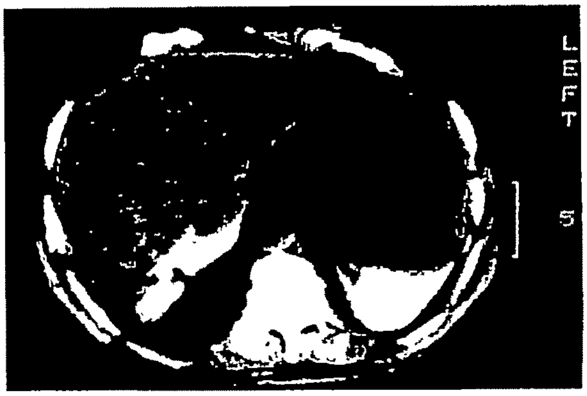

Fig. 1 Computed tomogram of the upper abdomen showing evidence of previous surgical treatment of a liver hydatid cyst and a large splenic cyst

Discussion

Nowdays, attempted preservation of the spleen is mandatory when treating benign disease. Cyst enucleation and marsupialization (Posadas–Dwe method) has also been reported, with good results[3,4]. However, with partial cystectomy with omentoplasty and drainage, operating time is shorter, manipulation of the spleen is less and the complication rate is probably lower in the hands of general surgeons.

Hydatid cyst of the spleen is a very rare condition and preservation of the spleen should always be tried, especially in children[3,5]. Splenectomy should be carried out only when local conditions dictate or technical mishaps occur.

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Oesophageal and cardia function in patients with paraoesophageal hiatus hernia

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Background The decision to add an antireflux procedure when a paraoesophageal hernia is repaired is still controversial. The aim of this study was to investigate oesophageal and cardia function in these patients to verify whether fundoplication was needed.

Methods Eighteen patients with paraoesophageal hernia were evaluated by oesophageal manometry, 24-h pH monitoring, endoscopy and barium swallow. All patients underwent surgery including antireflux fundoplication. Fourteen patients with sliding hernia plus reflux disease and 16 healthy volunteers formed the control groups.

Results Patients with paraoesophageal hernia had a shorter lower oesophageal sphincter and a greater acid exposure than healthy controls ($P < 0.05$). Fifteen of 18 patients had either abnormal acid exposure and/or a defective lower oesophageal sphincter at manometry. Postfundoplication symptoms were observed in only one of 16 patients at 6 months' follow-up.

Conclusion Since 15 of 18 patients had abnormal acid exposure or were considered prone to developing gastro-oesophageal reflux disease because of a defective lower oesophageal sphincter, this study strongly supports the need to add an antireflux operation to hernia repair.

Paraoesophageal hiatus hernia is a relatively uncommon abnormality of the diaphragmatic hiatus; the clinical picture and associated complications are quite distinct from those of the more common sliding hernia[1]. It has been estimated that they represent only about 2–19 per cent of all radiologically-observed hiatus hernias[2,3] and from 3 to 8 per cent of the hiatus hernias requiring surgical repair[4,5]. Paraoesophageal hiatus hernias differ from sliding hernias in that they maintain the cardia beneath the diaphragm and have the fundus and most of the body of the stomach dislocated into the mediastinum[6]. An intermediate type, the so-called mixed or type 3 hernia, has also been described and comprises a simultaneous herniation of the whole cardiac junction through the hiatal defect, but with the fundus and the greater curvature of the stomach as the leading point of herniation[7,8]. Paraoesophageal and mixed hernias have a much larger hiatal defect than sliding hernias, and a peritoneal sac is always found.

For the purpose of this study, hiatus hernias were considered as paraoesophageal when the fundus and the greater curvature of the stomach were herniated into the posterior mediastinum, lying at a point higher than the oesophagogastric junction[9], and when a peritoneal sac was clearly evident at surgical dissection. This definition therefore included both true and mixed types of paraoesophageal hernia.

It is generally accepted that the indication for the surgical repair of a paraoesophageal hernia is the diagnosis itself, not the presence or absence of symptoms. Failure to take early action may result in life-threatening complications such as gastrointestinal bleeding or strangulation of the herniated stomach, which are associated with an unacceptable mortality and morbidity rate. Surgery consists of replacing the stomach in the abdominal cavity and repairing the crural defect. There is no consensus as to whether an antireflux procedure should be added routinely.

Since paraoesophageal hernias are relatively rare and may require emergency procedures, few studies have attempted to assess oesophageal function in such patients and conclusions concerning whether a fundoplication is called for are often based merely on symptomatic or endoscopic considerations[10]. The aim of this study was to evaluate oesophageal and cardia function in 18 consecutive patients with paraoesophageal hernia and to assess outcome after surgical repair that routinely included an antireflux procedure.

Patients and methods

From January 1988 to December 1995, 98 operations were performed for hiatus hernia and/or gastro-oesophageal reflux disease (GORD). Eighteen of the patients were diagnosed as having a pure paraoesophageal hernia (four) or a mixed hernia (14) and thus formed the study population. There were six men and twelve women with a median age of 65 (range 41–75) years. Height and body-weight were recorded at presentation. Symptoms were investigated using a standard questionnaire and patients were requested to state their main symptom; heartburn and regurgitation were scored separately. The final score resulted from the sum of values scored for severity (0, no symptom; 1, symptom not reported spontaneously by the patient; 2, symptom reported spontaneously by the patient; 3, symptom interfering with daily life) and frequency (0, never; 1, occasionally; 2, every week; 3, two to three times a week; 4, every day). All patients were evaluated before operation by means of a barium swallow, upper gastrointestinal endoscopy (with oesophagitis classified according to Tytgat[11]), oesophageal manometry and 24-h pH monitoring. Patients were asked to undergo the same tests 1 month (barium swallow) and 6 months after surgery. Thereafter, patients had yearly clinical follow-up.

Stationary oesophageal manometry was performed as described elsewhere[12,13]. If it was impossible to pass the manometric probe into the stomach through a twisted oesophagogastric junction, a guidewire was inserted during endoscopy and

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used to position the probe correctly through the cardia. The distance from the nostril to the upper border of the lower oesophageal sphincter (LOS) was measured. Patients were considered as having a manometrically defective LOS when sphincter pressure at the respiratory inversion point, abdominal length and/or overall length of the sphincter fell below the 5th centile of the control group (7 mmHg, 18 mm and 29 mm respectively). Twenty-four-hour pH monitoring was performed as described elsewhere[14]. Patients were considered to have GORD if at least two of the parameters considered were in excess of the 95th centile of values for the control population. Sixteen healthy volunteers (ten men, six women; median age 33 (range 23–80) years) and the most recent 14 consecutive patients with hiatus hernia and GORD (eight men, six women; median age 42 (range 16–78) years) formed the control groups.

In all but one of the patients, surgery was performed transabdominally; in five patients it was done laparoscopically. After replacing the stomach in the abdomen crural repair was performed posteriorly; an anterior repair was also added in a few patients. Care was taken to remove all of the peritoneal sac. A Nissen–Rossetti fundoplication completed the operation in 16 patients. Collis gastroplasty and Nissen fundoplication were performed in one patient with a short oesophagus, and one patient with poor oesophageal motility underwent posterior hemifundoplication (Toupet).

Statistical analysis

Data are expressed as median (range). Non-parametric tests (Kruskal–Wallis test, Mann–Whitney *U* test and Wilcoxon signed rank test, as appropriate) were used to compare the groups and to compare preoperative and postoperative data within the same group. Fisher's exact test was used to compare categorical data.

Results

The median age of patients with paraoesophageal hernia was significantly higher than that of patients with sliding hernia ($P<0{\cdot}05$). No differences in height and bodyweight were found between the paraoesophageal hernia and sliding hernia groups.

Barium swallow demonstrated complete herniation of the stomach into the mediastinum in four patients. One-third of the patients (six of 18) had no symptoms and were referred to the specialist for investigation of iron-deficiency anaemia: the hernia was diagnosed during subsequent investigations. The main symptoms reported by the symptomatic patients were heartburn in four, regurgitation in three and some kind of swallowing difficulty in three; one patient complained of thoracic pain (hernia was suspected after standard chest radiography) and one of early satiety. *Fig. 1* shows the scores for heartburn and acid regurgitation in patients with paraoesophageal hernia and in those with sliding hernia and GORD. Endoscopic oesophagitis was observed in seven patients (grade 1, $n=1$; grade 2, $n=5$; grade 3, $n=1$). The incidence of endoscopic oesophagitis was lower in patients with paraoesophageal hernia than in patients with sliding hernia and GORD (seven of 18 *versus* 11 of 14; $P<0{\cdot}05$).

The distance of the LOS from the nostril proved significantly shorter in patients with paraoesophageal hernia than in those with sliding hernia and GORD, i.e. 33 (28–40) *versus* 40 (34–48) cm ($P<0{\cdot}01$). No difference in the distance of the LOS from the nostril was observed between patients with true paraoesophageal hernia and those with a mixed type (34 *versus* 32 cm).

Table 1 shows the manometric findings for the LOS. As a group, patients with paraoesophageal hernia had significantly shorter overall and abdominal LOS lengths than healthy subjects, whereas the LOS pressure was not significantly lower than that in controls. Twelve patients had a manometrically defective cardia. No differences were observed as regards the percentage of peristaltic contractions. *Table 2* shows the 24-h pH monitoring parameters in the three groups. Patients with paraoesophageal hernia were more exposed to a pH of less than 4 (expressed both as a percentage of the time for the whole test and as a percentage of the time spent in a supine position) than healthy controls. However, when patients were considered individually, only nine patients had

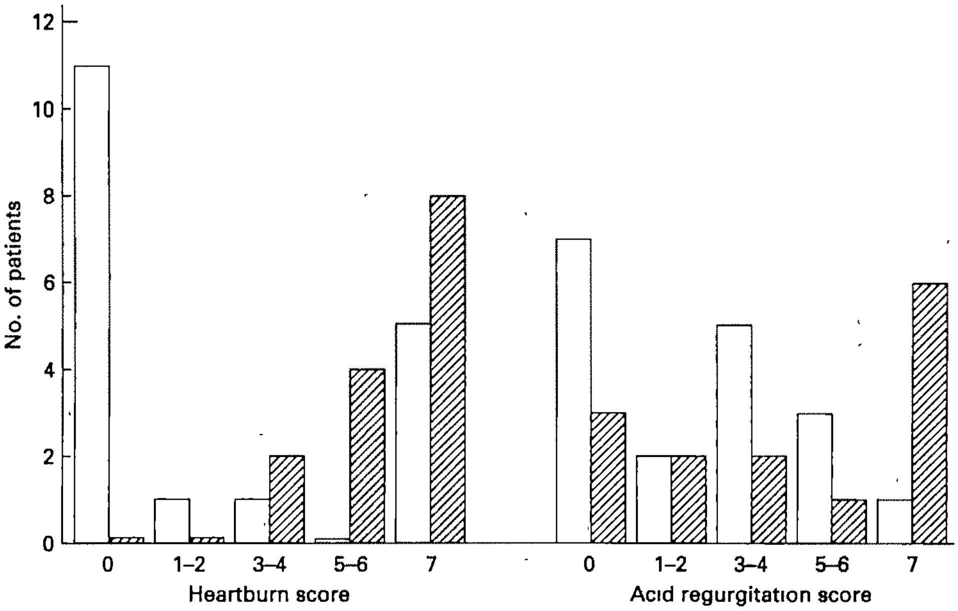

Fig. 1 Scores of the typical symptoms of gastro-oesophageal reflux disease (heartburn and acid regurgitation) in patients with paraoesophageal hernia (☐, $n=18$) or sliding hernia plus gastro-oesophageal reflux disease (▨, $n=14$)

Table 1 Manometric characteristics of the lower oesophageal sphincter

	Paraoesophageal hernia		Sliding hernia and GORD (*n* = 14)	Normal controls (*n* = 16)
	Before operation (*n* = 18)	After operation (*n* = 13)		
Pressure (mmHg)	7 (2–22)	11 (6–29)†	7 (2–18)*	12 (6–20)
Overall length (mm)	25 (10–70)*	37 (23–70)†	26 (14–63)*	35 (27–48)
Abdominal length (mm)	15 (0–27)*	24 (15–58)†	14 (10–30)*	25 (16–36)

Values are median (range). GORD, gastro-oesophageal reflux disease. *$P < 0·05$ *versus* normal (Kruskal–Wallis and Mann–Whitney *U* tests); †$P < 0·05$ *versus* before operation (Wilcoxon signed rank test)

Table 2 Oesophageal acid exposure at 24-h pH monitoring

	Paraoesophageal hernia		Sliding hernia and GORD (*n* = 14)	Normal controls (*n* = 16)
	Before operation (*n* = 18)	After operation (*n* = 13)		
Percentage of total time pH < 4	2·6 (0–36·1)*	0·1 (0–11·8)†	9·2 (1·4–29·3)*	1·1 (0–5·0)
Percentage of upright time pH < 4	1·9 (0–50·6)	0·2 (0–9·5)	5·7 (0·1–25·9)*	1·0 (0–9·0)
Percentage of supine time pH < 4	3·6 (0–36·9)*	0·0 (0–19·2)†	7·2 (3·7–34·8)*	0·1 (0–0·4)
No. of episodes pH < 4	18 (0–80)	2 (0–62)†	78 (4–504)*	19 (5–40)
Duration of longest episode (min)	13·5 (0–185)*	1 (0–61)	30 (11–55)*	2 (0–23)
No. of reflux episodes > 5 min	2 (0–18)*	0 (0–5)†	5 (1–23)*	0 (0–8)

Values are median (range). GORD, gastro-oesophageal reflux disease. *$P < 0·05$ *versus* normal (Kruskal–Wallis and Mann–Whitney *U* tests); †$P < 0·05$ *versus* before operation (Wilcoxon signed rank test)

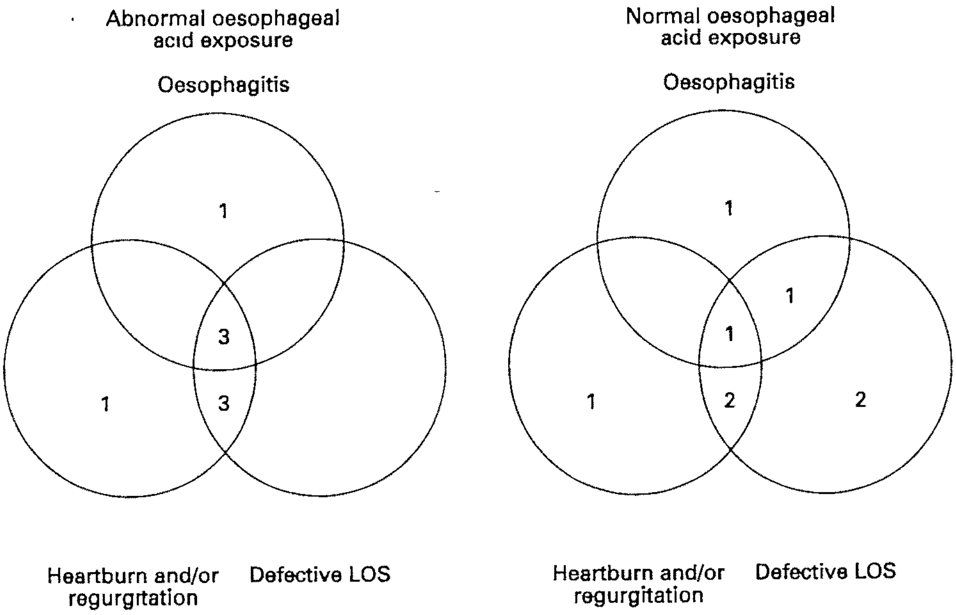
Abnormal oesophageal acid exposure
Oesophagitis
1
3
1
3
Heartburn and/or regurgitation
Defective LOS
Normal oesophageal acid exposure
Oesophagitis
1
1
1
1
2
2
Heartburn and/or regurgitation
Defective LOS

Fig. 2 Distribution of symptoms of gastro-oesophageal reflux disease, oesophagitis at endoscopy, and manometrically defective lower oesophageal sphincter (LOS) in patients with paraoesophageal hernia, with ($n = 9$) and without ($n = 9$) abnormal acid exposure of the distal oesophagus at 24-h pH monitoring. In both groups six of nine patients had a manometrically defective LOS. One patient in each group had none of the above conditions

abnormal acid exposure. *Fig. 2* integrates results on the presence of GORD symptoms, oesophagitis at endoscopy and oesophageal manometry in patients with and without abnormal acid exposure identified by 24-h pH monitoring. In both groups (i.e. those with and those without abnormal acid exposure), two-thirds of patients had a manometrically defective LOS. Overall, 15 of 18 patients had abnormal gastro-oesophageal reflux and/or a defective LOS at manometry. No differences were observed in the distribution of abnormal acid exposure in the distal oesophagus between patients with 'pure' or type 1 paraoesophageal hernia (two of four) and those with a mixed or type 3 hiatus hernia (seven of 14).

There were no deaths related to surgery. Follow-up for a median 6 (2–25) months was obtained in all patients. Two developed an incisional hernia after operation. Two complained of transient dysphagia that regressed spontaneously within 8 weeks. Chronic anaemia resolved in all patients who had presented with this finding. A recurrent hiatus hernia due to partial slipping of the fundoplication in the mediastinum was observed in two patients; one was asymptomatic and the other complained of heartburn and had a positive 24-h pH monitoring test. One patient complained of mild gas-bloat syndrome. The other patients were asymptomatic.

Thirteen patients agreed to repeat the functional studies after operation. *Tables 1* and *2* show the data for oesophageal manometry and 24-h pH monitoring. One of the 13 patients, who was still complaining of heartburn, had abnormal acid exposure at pH monitoring.

Discussion

The aetiology of paraoesophageal hernia remains unknown. This condition is rare before the fourth decade, however, and the patients involved are generally 20 years older than those with a simple hiatus hernia[15], suggesting that this is an acquired disease, evolving over the years. The mechanism resulting in the formation of a paraoesophageal hernia is presumed to be related to a defect in the diaphragmatic crura which expands under the increased pressure of the abdomen. As this defect becomes larger, the most mobile portions of the stomach (the greater curvature and body) are drawn into the mediastinum by the negative intrathoracic inspiratory pressure. As the stomach continues in its pendulum motion between the abdomen and mediastinum, the posterior attachments of the oesophagogastric junction may be weakened, allowing the junction to migrate cephalad and giving rise to the mixed form of paraoesophageal hernia[1,16]. In contrast, Pearson and coworkers[17] recorded a clear history of reflux symptoms at some stage of the disease in 85 per cent of patients with paraoesophageal hernia and formulated the hypothesis that paraoesophageal hernia should be considered as an advanced stage of an ordinary sliding hernia. They also stated that, if accurate measurements are performed, the oesophagogastric junction will be found in its normal position in very few of these giant paraoesophageal hernias. In the present patients, it was possible to document the progressive enlargement of two small sliding hernias in an intrathoracic upside-down stomach and in a large mixed hernia, over a period of 10 and 7 years respectively. One patient reported a change in symptoms characterized by the disappearance of pyrosis, replaced by a sensation of early satiety, while heartburn became more severe in the other.

Further support for Pearson's theory comes from the manometric finding of a shorter distance to the upper border of the LOS from the nostril in patients with paraoesophageal hernias in comparison with patients with hiatus hernia and controls, thus suggesting that some kind of oesophageal shortening and dislocation of the distal oesophagus into the mediastinum occurs during the course of the disease.

None the less, as the present study also confirms, patients with paraoesophageal hernia clearly have a lower incidence of typical gastro-oesophageal reflux symptoms and oesophagitis than patients with sliding hernias. However, the absence of typical symptoms of GORD or macroscopic oesophagitis does not rule out abnormal gastro-oesophageal reflux[18]. Abnormal exposure of the distal oesophagus to acid is demonstrated in 60 per cent of patients with paraoesophageal hernia[13]. This figure is consistent with the present data (nine of 18 patients) and suggests that GORD occurs more often in such patients than might be suspected on the basis of symptoms and endoscopic findings alone. Furthermore, a manometrically defective LOS was observed in two-thirds of patients with paraoesophageal hernia, with an equal distribution between cases with and without GORD. It has been demonstrated that a manometrically defective LOS exists in about 50 per cent of patients with GORD[19] and, when this is the case, it is associated with failure of antireflux medication[20]. The presence of a defective LOS is rarely observed in patients without GORD, making it a highly specific marker for the disorder[21].

The reason why so many patients with paraoesophageal hernia and a manometrically defective cardia do not have abnormal GORD is not clear. In some patients, it may be that the herniated gastric body acts as a flap, preventing any abnormal gastro-oesophageal reflux; this flap mechanism may also explain reported difficulties in passing an endoscope or a manometric probe through the cardia[22]. When the stomach is restored to its normal intra-abdominal position, however, the defective LOS cannot prevent acid reflux, as shown by the considerable number of patients with symptoms of GORD (61 per cent) after crura repair alone by comparison with those who also underwent an antireflux procedure (21 per cent)[9]. In this study 15 of the 18 patients had reflux or were prone to develop reflux because of a defective manometric LOS. It is highly likely that such patients will benefit from fundoplication and that an antireflux procedure may be safely avoided in only a minority of such cases.

Although there were no emergency presentations in the present series, this possibility has been well documented elsewhere and it is generally agreed that early surgical repair is needed when a paraoesophageal hernia is diagnosed[5,16]. A variety of surgical procedures has been described in the past, the key points of the operation being reduction of the stomach, excision of the sac and closure of the hiatal defect. To repair the hiatus, a suture anterior to the oesophagus[2,23], or posterior, so that the two crura can be included[17], or a patch with a prosthetic mesh[24,25], have been proposed.

The anterior repair is advocated because it is simple and requires no dissection of the distal oesophagus, which disrupts the posterior phreno-oesophageal membrane and destroys the natural antireflux barrier. However, in this series, as in Pearson's, the oesophagogastric junction is more or less dislocated from its normal position and only a short segment of distal oesophagus, or no oesophagus at all, is usually present in the abdominal cavity. In the authors' experience, dissection of the distal oesophagus is a necessary step to return an adequate length of the oesophagus to the abdominal cavity, regardless of the type of crura repair. When dissection of the distal oesophagus is performed, there is an additional reason for fundoplication, since the anatomical antireflux barrier is disrupted and a new mechanism is necessary. Moreover, the fundoplication itself forms a bulky upper stomach below the repair, which is less likely to herniate back into the chest and tends to fix the stomach so that recurrent volvulus becomes unlikely. Surgeons who do not favour routine antireflux repair raise the problem that post-fundoplication symptoms may outweigh the potential benefit of obtaining perfect reflux control[22]. This does not seem the case, in these patients at least, since transient dysphagia was observed in only two patients and gas-bloat syndrome in one. The reason for this low incidence of postfundoplication symptoms probably lies in the considerable mobility of the gastric fundus that allows for the fashioning of a very floppy fundoplication.

In conclusion, patients with paraoesophageal hernia have a high incidence of GORD; they often have a defective LOS, even when there is no apparent abnormal acid exposure; and in the majority of these patients the distal oesophagus is displaced into the mediastinum, thus requiring complete dissection to return the distal part to the abdomen. These conditions confirm that fundoplication should be performed routinely in patients with paraoesophageal hernia.

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Short note

Randomized controlled trial of an H_2-receptor antagonist in gastric cancer

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The competence of the immune system is suppressed in patients with gastrointestinal cancer, especially in those with advanced disease. Furthermore, major cancer surgery produces immunosuppression[1]. Several reports suggest that H_2-receptor antagonists have an immunostimulatory effect[2,3]. Furthermore, Tonnesen *et al.*[4] reported a significant increase in median survival of patients with gastric cancer treated with cimetidine. Clearly, if confirmed, these observations would be of major clinical importance. The results of a prospective, randomized, double-blind, placebo-controlled trial of an H_2 receptor antagonist in patients with gastric cancer are reported.

Patients and methods

Between March 1991 and March 1994, 159 patients, presenting to 13 hospitals in the west of Scotland, who underwent laparotomy for gastric cancer were enrolled in the study. Patients were randomized to receive either ranitidine (n = 79) or placebo (n = 80). Intravenous treatment was commenced at induction of anaesthesia (50 mg ranitidine or placebo) and continued (50 mg ranitidine or placebo three times daily) until the patient was able to tolerate adequate oral intake. Thereafter, patients received oral ranitidine 150 mg or placebo twice daily for a minimum period of 2 years or until death. Patients were followed at 3-month intervals. Dates of suspected or proven tumour recurrence and death were documented. Statistical analysis was based on the log rank test, with life tables constructed using the Kaplan–Meier method. The protocol was approved by the local ethics committees. All patients gave written informed consent.

Results

Patients in the treatment and placebo groups were similar in age, sex, weight, site of tumour, type of surgery, whether or not the surgery was regarded as curative and tumour stage. Compliance was 74 per cent at 1 year and 64 per cent at 2 years. Follow-up ranged from 2 to 4·8 years. Survival did not differ significantly between the groups (*Fig 1*) (χ^2 = 0·24, 1 d.f., P = 0·62). The relative hazard for ranitidine *versus* placebo was 1·09 (95 per cent confidence interval 0·77–1·55). The estimated median(s.e.) survival was 280(81) days for the ranitidine group and 344(71) days for the placebo group.

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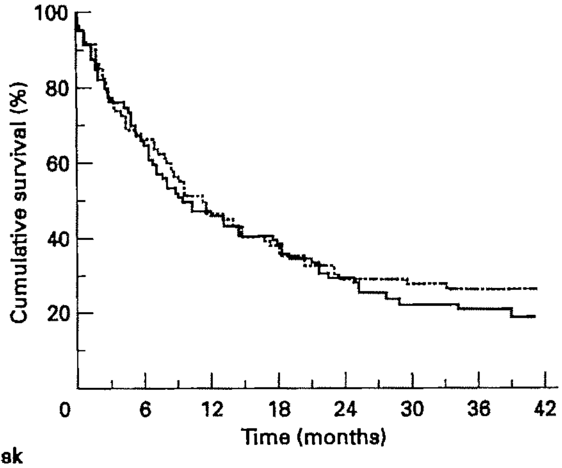

No. at risk	0	6	12	18	24	30	36	42
Ranitidine	79	52	36	30	22	13	12	10
Placebo	80	53	37	30	22	19	16	15

Fig. 1 Survival curve of patients receiving either placebo (- - -) or ranitidine (———). There was no difference in survival between the groups (P = 0·62, log rank test)

Discussion

Clearly it was disappointing that the results of Tonnesen *et al.*[4] could not be reproduced although the study design was very similar and the agent used was a potent H_2-receptor antagonist. Furthermore, in a small parallel study of 28 patients deemed unsuitable for laparotomy, a similar non-significant trend against ranitidine was observed (relative hazard 1·75, 95 per cent confidence interval 0·78–3·89). The reasons for this are unclear. It may be that the numbers in the present series were insufficient to demonstrate a survival advantage in the treated group although they were comparable to those in Tonnesen *et al.*'s study[4]. Alternatively, it may be that ranitidine is less effective than cimetidine in its immunostimulatory properties. Indeed, Hahm and co-workers[5] reported that the immunostimulatory effects of ranitidine and famotidine on peripheral blood mononuclear cells in patients with gastric cancer were less than those of cimetidine. It is concluded that ranitidine does not affect survival in gastric cancer.

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Short note

Inguinal cord lipoma

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Fat is often present in the inguinal canal between the spermatic vessels or in separate masses which surgeons usually refer to as lipomas. Ponka[1] recognized finger-like protrusions of adipose tissue along the path of the spermatic cord but thought they represented a variety of indirect inguinal herniation and termed them lipomas. Other textbooks make little or no reference to such protrusions. Differentiating between protrusions and lipomas may be important clinically and medicolegally.

Methods

A prospective series of 140 inguinal hernias in 129 patients was studied. A fatty swelling was deemed significant if it was possible to separate it from the fat accompanying the testicular vessels If the fatty swelling was continuous through the deep inguinal ring with extraperitoneal fat it was called a protrusion. If confined to the inguinal canal with no connection to the extraperitoneal fat it was termed a lipoma.

Results

Sixty-nine hernias were on the right, 49 on the left and 11 were bilateral. Fatty protrusions were found in 46 hernias (33 per cent), 24 (30 per cent) on the right and 22 (37 per cent) on the left. Of the 11 patients with bilateral hernias one had a unilateral and five had bilateral protrusions. Protrusions were found with equal frequency in all varieties of inguinal hernia. In three patients the only abnormal finding was a fatty protrusion. A number of other observations were made during the study: three patients had fatty protrusions which had been diverted between the layers of the conjoint tendon or beneath a layer of fascia over the surface of the conjoint tendon; only one true lipoma of the cord was found; one patient had an indirect sac with a separate large fatty protrusion through a small posterior wall defect; and between two and four separate protrusions occurred in seven hernias.

Discussion

Only one true lipoma was found in this study. It is likely, therefore, that the fatty protrusions found at hernia repair are extraperitoneal fat extruded through the deep inguinal ring. Since these fatty protrusions occur in association with all varieties of hernia the forces causing the hernia may also cause extraperitoneal fat extrusion. These findings may be of importance medicolegally when the presence of a fatty protrusion without a hernia sac could have the same significance as a hernia sac. Fatty protrusions between the layers of the conjoint tendon may be missed or misinterpreted during hernia surgery.

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British Journal of Surgery 1997, 84, 1170–1179

Correspondence

Osmotic therapy for acute irreducible stoma prolapse

Letter 1

Sir

As a previous trainee at this hospital, Mr Fligelstone (*Br J Surg* 1997; 84: 390) will not mind my informing readers that the above approach is not a new one. I first had the opportunity of using it in a similar patient to that described after reading an article describing its value[1].

Over the past 3 to 4 years I have used this osmotic 'poultice' on various oedematous appendages such as prolapsed stomas, paraphimosis and prolapsed haemorrhoids. One garrulous, artistic lady with haemorrhoids suggested an even sweeter approach to the problem. She brought to my attention the fact that icing sugar, as used in cake decorating, is even more hydrophilic than ordinary granulated sugar. This is now my preferred solution to these slippery problems.

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1 Myers JO, Rothenberger DA. Sugar in the reduction of incarcerated prolapsed bowel: report of two cases. *Dis Colon Rectum* 1991; 34: 416–18

Letter 2

Sir

I read with interest the article by Mr Fligelstone and colleagues (*Br J Surg* 1997; 84: 390). I thought the technique was so interesting, in fact, that we published it in 1991[1]. As noted in our article, farmers have apparently used salt or sugar to reduce prolapse, and veterinary textbooks describe the technique for reduction of prolapse in dogs, cats and horses.

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Retrosternal goitre: a wider view

Sir

I was intrigued to read this Surgical Workshop recommending the use of partial claviculectomy for offering easier access to retrosternal goitre (*Br J Surg* 1997; 84: 403). The authors remark on the good function and cosmetic recovery from this procedure, but the description is of a destructive procedure, and one cannot but question its usefulness. Retrosternal goitres that are not fixed in the chest by malignancy can almost invariably be removed from above. The authors suggest that the advantage of the claviculectomy is that it allows the depth to which an index finger can be inserted into the mediasternum to increase from 6 to 9 cm. Might I respectfully suggest that if the authors have difficulty extracting retrosternal goitres from the neck incision the use of one or two dessert spoons allows the mediastinum to be entered to a distance of 12 cm and their shape enables them to be insinuated around goitres too tightly wedged for the insertion of a finger.

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Prospective comparison of laparoscopy, ultrasonography and computed tomography in the staging of gastric cancer

Sir

I read with interest the article by Mr Stell *et al.* (*Br J Surg* 1996; 83: 1260–2) They compared sensitivity and specificity by means of the 'uncorrected χ^2 test', and to compare the sensitivity of laparoscopy *versus* ultrasonography they constructed a 2×2 contingency table taking into account that hepatic metastases were histologically proven in 27 patients.

	True positive	False negative	Total
Laparoscopy	26 (a)	1 (b)	27 (m_1)
Ultrasonography	10 (c)	17 (d)	27 (m_2)
Total	36 (n_1)	18 (n_2)	54 (N)

From this table, $\chi^2 = (ad - bc)^2 N^2/(n_1 n_2 m_1 m_2) = 21\ 33$ as shown at the bottom of *Table 2*.

The use of the χ^2 test is inappropriate because the study is not dealing with independent proportions. Although the conclusions of Stell *et al.* can be considered correct on the basis of the higher values of sensitivity and specificity, they are not supported by the results of a correct and sound statistical analysis.

It is important to submit every article to a statistical consultant to avoid this error and reduce the 'propagation of the error' to a minimum.

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Latex allergy: an emerging health hazard for operating theatre staff

Sir

Allergy to latex itself (*Br J Surg* 1997; 84: 289–90) is only part of the picture of allergy to surgical gloves; accelerating and vulcanizing agents are also guilty of causing allergic reactions The opinion of a dermatologist with an interest in contact dermatology is essential and patch testing can determine which agent is the allergen. Once this is known, gloves can be used that do not use such agents. Closer co-operation between occupational health, dermatologists, medical staffing and theatre ordering departments would make starting in a new post more straightforward.

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Matrix metalloproteinases

Sir

We read with interest the comprehensive Review by Mr Parsons *et al.* (*Br J Surg* 1997; 84: 160–6). We would like to highlight certain interesting aspects regarding the activation of pro-matrix metalloproteinase (MMP)-2. In contrast to other MMPs, pro-MMP-2 is not activated by proteases like plasmin[1] and, until the isolation of membrane-type (MT) 1-MMP, 'cell membrane fraction' was generally believed to be the main activator but MMP-1 and 7 have also recently been shown to activate pro-MMP-2[2]

Sato *et al.*[3] had immunolocalized MT1-MMP protein to the membrane of lung adenocarcinoma cells When using *in situ* hybridization in human colon, breast, head and neck, and lung adenocarcinomas, messenger RNA (mRNA) for MT1-MMP was also localized to the stromal fibroblasts[4,5]. In squamous cell lung cancers the transcripts were localized to both the stromal and cancer cells[5]. This disparity between the localization of the MT1-MMP protein (which has a transmembrane domain and without which it cannot activate MMP-2) and its mRNA does not lend itself to any simple explanation. One explanation is the possibility that mRNAs from different cells have varying degrees of susceptibility to tissue fixation with inaccurate localization.

The promoter region of the MMP-2 gene, in contrast to other MMPs, lacks the TATA and TRE sequence but contains multiple SP-1 binding sites[6]. It would, therefore, appear that regulation of MMP-2 secretion is different from other MMPs. Hence, coexpression of MMP-2 and MT1-MMP genes, whether it is in the stromal or cancer cells, would ensure closer co-operation (and also tight regulation) between the proteolytic enzyme and its activator.

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Peritoneal seeding of pancreatic head carcinoma following percutaneous transhepatic drainage and stenting

Sir

We read with interest the report by Doctor *et al.* (*Br J Surg* 1997; 84: 197) of a patient presenting with obstructive jaundice secondary to carcinoma of the head of pancreas, who underwent preoperative percutaneous external biliary drainage and transhepatic biliary stenting Secondary peritoneal deposits developed along the catheter tract, an event not previously reported. We have recently observed the same phenomenon in an elderly patient with irresectable adenocarcinoma of the pancreas who underwent percutaneous stenting. The patient subsequently developed duodenal obstruction and at operation there was no evidence of secondary spread except for the presence of small peritoneal deposits in the tract of the percutaneous stent. This highlights the potential for malignant seeding of pancreatic tumour cells along transhepatic catheter tracts.

Percutaneous transhepatic stenting is usually reserved for jaundiced patients with advanced irresectable disease in whom a transduodenal approach has failed. These patients are unlikely to survive more than a few months and therefore malignant seeding is clinically irrelevant We wonder if this phenomenon is more frequent than previously recognized. The development of peritoneal deposits as a result of percutaneous biliary drainage may preclude excision of an otherwise resectable tumour. It is generally accepted that percutaneous biopsy is contraindicated in patients with operable carcinoma of the pancreas for fear of tumour seeding along the needle tract[1], and we agree that preoperative percutaneous stenting should also be avoided in those patients with potentially resectable lesions.

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Laparoscopic and conventional repair of groin disruption in sportsmen

Sir

We were interested to read the report by Mr Ingoldby (*Br J Surg* 1997; 84. 213–15) We would be interested to know how many of these patients had a proven inguinal hernia, as this is a condition not found in our series[1]. Our view is that this is an entrapment neuropathy caused by damage to the external oblique muscle and we have not found any damage to the conjoint tendon, as previously described.

We would be interested to know the long-term results of this hernia repair surgery We would favour the simpler approach previously described and our long-term follow-up confirms that this is a successful technique

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1 Foster ME, Ziprin P. Gilmore's groin – or is it? *Br J Sports Med* 1995; 29· 1–3.

Author's reply

Sir

I am grateful for Messrs Foster and Ziprin's interest in my paper. There is dispute as to whether persistent pain in the groin preventing sporting activity is due to external oblique disruption alone or damage to the conjoint tendon apparatus. The experience described (*Br J Surg* 1997; 84: 213–15), using a laparoscopic approach to repair the conjoint tendon but not the external oblique, strongly suggests that conjoint tendon repair alone is successful. For this reason I consider that isolated external oblique damage is unlikely to be a common cause of this condition. None of the patients in the series had an inguinal hernia but some degree of distension of the conjoint tendon apparatus was usually apparent on laparoscopy, compatible with conjoint tendon damage.

The current longest follow-up in my personal series is 4·5 years and I have no long-term data on the relative merits of any particular technique. As reported there has been one recurrence of pain in each group to date.

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Letter 2

Sir

We read with interest the single-surgeon experience of inguinal surgery in sportsmen (*Br J Surg* 1997; 84: 213–15) which asserted that 'laparoscopic groin repair caused less pain than conventional surgery and allowed earlier return to sport'. While the diagnosis of persistent inguinal pain in sportsmen may be difficult, we are concerned that Mr Ingoldby did not investigate the cause of the pain using herniography, a simple, inexpensive and reliable method to establish the diagnosis of a hernia before surgery[1–3]. The consecutive statements that 'none had a visible hernia. Eleven of the 28 patients had a cough impulse noted in the inguinal canal' suggest that herniography could have been extremely useful in establishing the diagnosis in one-half of these sportsmen. One large series demonstrated a hernia in the symptomatic groin of 84 per cent of sportsmen where the diagnosis was uncertain on clinical grounds alone[3].

The non-random self-selection of laparoscopic *versus* open repair and associated differences in time to resume sport and wound pain (particularly in the absence of any objective measurement of wound pain or mention of analgesic use) may reflect the increased motivation of sportsmen in season rather than any real difference between the surgical techniques used. Together, these factors cast doubt on whether the reported statistical differences are of true clinical significance. We acknowledge that, in a conventional population, unilateral laparoscopic hernia repair can result in a quicker recovery[4]. While a randomized study could answer this question in sportsmen, patient demand fuelled by studies such as that reported by Mr Ingoldby may make a definitive answer elusive.

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Author's reply

Sir

I was interested to read the comments of Messrs Nagy and Thompson. I agree that the diagnosis of groin pain in sportsmen can be difficult and a proportion of patients with pain will have an undiagnosed hernia. The study was concerned with patients with persistent groin pain despite the absence of a hernia, and patients with occult indirect hernias were excluded from the series. Whether herniography has a role to play in the diagnosis of conjoint tendon disruption remains to be determined. I agree that a randomized trial would be desirable to confirm the advantages but it is unlikely to be performed in view of the strong views held by many sportsmen on the merits or otherwise of laparoscopic surgery.

The paper aimed to assess whether a less painful surgical technique was as effective in relieving pain as conventional methods, and to demonstrate whether posterior wall repair alone was as effective as the anterior wall repair advocated by Gilmore[1]. I feel the data demonstrate that a posterior wall repair is all that is required in this form of groin disruption.

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1 Gilmore OJA. Gilmore's groin: ten years experience of groin disruption – a previously unsolved problem in sportsmen. *Sports Medicine and Soft Tissue Trauma* 1991; 3: 12–14.

Extending the role of breast-conserving surgery by immediate volume replacement

Sir

We read with interest the paper by Mr Raja and colleagues (*Br J Surg* 1997; 84: 101–5) regarding a 'novel' method of immediate volume replacement after breast-conserving surgery. The authors state that they adapted the latissimus dorsi muscle harvest described by Noguchi *et al.*[1–3] to provide immediate volume replacement. We see no discernible difference between the method described by Noguchi *et al.* and the 'adaptation' described by Raja *et al.*, nor did the latter authors discuss how the procedure was adapted. The latissimus dorsi flap was first introduced by Tanzini in 1894 (as described by Maxwell[4]) as a method of resurfacing the radical mastectomy defect and has become the most versatile flap in plastic and reconstructive surgery. Immediate breast volume replacement using the latissimus dorsi muscle was also described by Papp *et al.*[5] in 1988 after subcutaneous mastectomy and by Zoetmulder *et al.*[6] in 1993 after breast-conserving surgery.

Furthermore, cosmetic outcome detailed in the article was assessed by direct measurement of breast retraction assessment (BRA) and panel assessment. Use of the BRA may produce numbers but provides an inaccurate evaluation of cosmetic outcome. BRA greater than 3·5 was determined to be cosmetic failure. For example, a deviation of the nipple 2·5 cm laterally and inferiorly would lead to a BRA of over 3·5. In a large-volume breast, this would not necessarily mean that there is a cosmetic failure because some asymmetry occurs naturally. On the other hand, a perfect alignment of the nipple position can coexist with a severe deformity, especially when the defect is located in the lower quadrant. The invalidity of BRA was documented in the discrepancies between BRA results and the findings of a 15-member evaluation panel. The panel found a cosmetic failure rate of 10 per cent in the reconstructed group and 11 per cent in the non-reconstructed group. The BRA results showed a 10 per cent cosmetic failure using the latissimus dorsi 'mini' flap (reconstructed) *versus* 34 per cent with only wide local excision (non-reconstructed) The visual result should be the determining factor for the patient since psychological trauma depends on how the patient perceives herself and how she is, or believes she is, perceived by others. If a panel perceives only 1 per cent difference in cosmetic failure between the reconstructed and non-reconstructed group the success in reconstruction is questionable

To increase patient satisfaction, we recommend performing the procedure with two separate skin incisions. One incision measuring approximately 8 cm is inframammary, as in subcutaneous mastectomy, and the second 5–8-cm incision starts in the axilla, follows the anterior border of the latissimus muscle and runs alone the brassiere line as described by McCraw *et al.*[7] and Papp *et al.*[5]. One major advantage of these incisions is that both scars are less visible because of their location. In contrast, the S-shaped incision from the apex of the axilla to the inframammary skin crease is highly visible. Another advantage is that the latissimus dorsi muscle can be easily raised and transposed on its pedicle through a tunnel to the defect and defects in the lower quadrants can be easily covered. Using this procedure, enough available muscle would have allowed reconstruction of the defects in the inferior quadrants of the six 'difficult' patients.

In conclusion, we believe that, especially in small breasts, immediate breast-volume replacement with the latissimus dorsi muscle is a sophisticated method for avoiding deformity and patient trauma.

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Author's reply

Sir

Dr Wechselberger and colleagues fail to see any difference between our method of volume replacement and the original technique of Noguchi *et al.*[1], which was acknowledged and referenced in the text. Noguchi *et al.* performed a classical quadrantectomy together with resection of the overlying skin leading to a long visible frontal scar on the breast. Our technique was developed to overcome the inter-related problems of ugly frontal scars and volume loss, while facilitating the mobilization and harvest of the most bulky portion of latissimus dorsi. Important modifications to Noguchi's technique include: (1) a single lateral scar that is concealed by the anterior axillary fold, (2) extensive superficial and deep mobilization of the breast disc to allow very wide retromammary excision of breast tissue without skin loss or frontal scarring; (3) routine division of the latissimus dorsi tendon and serratus anterior branches of the thoracodorsal trunk to allow maximum transposition of the flap, while boosting its blood supply; and (4) enhanced volume replacement by harvesting subcutaneous fat which remains attached to the surface of the flap. Routine over-replacement of the volume resected compensates for a variable degree of postoperative flap atrophy.

Dr Wechselberger *et al.* rightly highlight the difficulty in evaluating cosmetic outcome. We felt it was important to use two different methods of cosmetic assessment rather than rely on the findings of one technique

The main purpose of volume replacement was to extend the role of breast-conserving surgery without incurring cosmetic penalties. Cosmetic outcome following volume replacement compared favourably with wide local excision alone, in spite of resecting significantly larger tumours and specimens in the group undergoing immediate reconstruction.

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Prospective randomized study of laparoscopic *versus* open colonic resection for adenocarcinoma

Letter 1

Sir

I read with interest the study of Dr Stage and colleagues (*Br J Surg* 1997; 84. 391–9) and would like to comment on their findings regarding interleukin (IL) 6 production. Apparently IL-6 median levels were three times as high in the group who underwent laparoscopic colectomy than in those who had open colectomy. This finding was characterized by the authors as unexpected and they attempted to explain it by implicating piroxicam given before operation While piroxicam can theoretically affect IL-6 in an indirect way by interfering with the prostaglandin metabolism, it has been shown that non-steroidal anti-inflammatory drugs decrease expression of IL-6[1] Besides that, piroxicam was given in both groups in this study so it is not possible to have biased IL-6 production in the laparoscopic group only

As Dr Stage and colleagues have pointed out, the immunomodulating effect of laparoscopic surgery remains uncertain, with a number of studies claiming that it causes less immunosuppression than open surgery while others have found no difference between the two.

IL-6 is a proinflammatory cytokine that is produced by most cells of the immune response as well as by fibroblasts and endothelial cells. It has been consistently found to rise dramatically in a number of surgical conditions such as major trauma, sepsis, burns as well as operative trauma. What is more important is that increased production of IL-6 has been repeatedly directly associated with morbidity and mortality[2]. IL-6 levels have also been associated with the duration of surgery[3] which in this study (as well as in others) is on average 50 per cent longer in the laparoscopic group than in the open colectomy group. What could be more important is that IL-6 has been directly associated with the extent of operative trauma[4]. In our opinion there is only one explanation for this study's findings: while laparoscopic colectomy causes less abdominal muscle trauma it causes more intraperitoneal trauma than open colectomy.

The question is, are there any clinical implications from this IL-6 rise or are we simply worrying over laboratory measurements? One cannot help thinking, however, that IL-6 has been proven to be a potent growth factor for malignant cells[5]. Port-site metastases after laparoscopic surgery (although not observed in this study) have been attributed to increased manipulation of tumours and cell implantation from high intraperitoneal pressure. Is there a chance that perioperative immunomodulation, as that expressed by increased IL-6 production, might play a role? The answer is to be obtained from long-term follow-up which we await with great interest.

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Letter 2

Sir

We wish to raise several issues regarding the randomized comparison of open *versus* laparoscopic colonic resection for cancer reported by Dr Stage and colleagues. Although patients were randomized to one or other treatment group, the results were not analysed on an intention-to-treat basis. Patients undergoing conversion were excluded and 'a new patient included after randomization to secure an appropriate number of patients'. The conversion rate was three in 18 patients and the main reason for conversion was said to be extensive tumour growth. Since no such exclusion criteria affected patients randomized to open surgery, failure to analyse the results on an intention-to-treat basis introduces a bias in favour of the laparoscopic group. For example, the three patients excluded due to conversion had a hospital stay of 7 days; this was 2 days longer than the median reported for the remainder of the laparoscopic group The principle of analysis by intention-to-treat in clinical trials is fundamental[1] and failure to do so potentially biases every parameter measured in the study.

The study is remarkable for the small number of complications recorded: two in the laparoscopic group and none in the open group. Despite no recorded complications at least one patient in the open group had a hospital stay of 30 days (*Table 2*). It was claimed that excision was equally radical in both groups on the basis of 'blinded' pathological evaluation, however it would be interesting to know whether a vascular stapler was used to divide the mesenteric pedicle in the laparoscopic operations as this gives the pathologist an obvious clue as to the technique employed. Other measures, such as pain and fatigue scores, may also be influenced by the lack of blinding[2].

In addition to potential biases the study is severely limited by its small size. Was a power calculation done to determine an appropriate sample size and, if so, what was it based on? The stated aims of the study were to 'compare laparoscopic and open colonic resection in a randomized fashion, with special reference to outcome, complications and immunomodulation'. With less than 20 patients in each arm the study is seriously underpowered to achieve its aims. In fact the risk of type I and type II errors probably exceeds the chances of detecting real differences in outcome[3]. The most important endpoint is long-term survival which was not addressed at all by this study. We estimate that to have 80 per cent power to detect a 10 per cent 5-year survival difference ($\alpha = 0{\cdot}05$, two-tailed test), a sample size of approximately 600 patients in each arm would be required.

The conclusion reached by Stage *et al.* that 'laparoscopic colonic resection is an acceptable and safe alternative to open procedures' cannot be sustained on the basis of a study containing methodological flaws and involving only 34 patients. The danger is that this study will be misinterpreted as having much greater scientific merit than it warrants simply because it has been called a prospective randomized study and published in a prominent surgical journal. We would echo the investigators call for further randomized studies, but stress that these must be properly designed and adequately powered to address the important issues of safety and efficacy[4].

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Authors' reply

Sir

We read the letter from Dr Papagrigoriadis with great interest. We agree that the increase in IL-6 is difficult to interpret in the laparoscopic group but most studies have shown that the systemic response and changes in cytokines are attenuated following laparoscopic surgery[1]. It is difficult to believe that the difference in IL-6 levels between groups may be attributed to the duration of surgery. The duration of surgery was not 50 per cent longer although the median value for laparoscopic resection was

150 min compared with 95 min for open surgery. The exact *P* value was 0·05 and in two earlier studies in open colonic surgery the median duration of surgery was 125–150 min[2,3]. In these two studies the IL-6 level was comparable to the level observed in the present study following open surgery. The explanation that laparoscopic colectomy causes more intraperitoneal trauma is speculative and not in agreement with other studies[1]. We have not observed any port-site metastases in the patients so far.

We do not agree with the observations of Drs McCall and Parry. The principal aim of this small randomized study was to evaluate the differences in systemic and immune responses and convalescence between the two groups. To secure appropriate numbers of patients in both groups for evaluation of these issues we found it necessary to accrue new patients for evaluation throughout the study period We agree that the three patients in the laparoscopic group who had to undergo conversion may be viewed as failures and this is acknowledged in the first part of the discussion.

The mesenteric pedicle was divided with either vascular stapler, metallic clips or polyglactin suture in the laparoscopic group. We agree that the study is too small to allow conclusions concerning long-term survival. We have concluded therefore that the differences between the two methods are not marked and laparoscopic surgery may not be completed in all patients. Obviously larger randomized studies are necessary to clarify whether long-term survival is different between the two methods.

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1 Kehet H, Nielsen HJ. Impact of laparoscopic surgery on stress responses, immunofunctions and risk of infectious complications *J Am Col Surg* (in press)
2 Schulze S, Sommer P, Bigler D *et al.* Effect of combined Prednisolone, epidural analgesia, and Indomethacin on the systemic response after colonic surgery. *Arch Surg* 1992; 127: 325–31
3 Schulze S, Andersen J, Overgaard H *et al.* Effect of Prednisolone on the systemic response and wound healing after colonic surgery. *Arch Surg* 1997; 132: 129–35.

Continuous double loop closure: a new technique for repair of laparotomy wounds

Sir

Dr Niggebrugge and colleagues present an elegant methodology in their study of post-laparotomy abdominal bursting pressures in rats (*Br J Surg* 1997; 84: 258–61) but the interpretation of their results is flawed and the relevance to clinical practice dubious.

Abdominal bursting pressure was measured immediately after closure of laparotomy wounds and differed with statistical significance when various suture techniques were used. The mean intra-abdominal pressures required to cause dehiscence were all greater than 190 mmHg and it is unlikely that such pressures would ever be encountered in patients. Flow in the capillaries of the abdominal wall and the inferior vena cava would have ceased long before these pressures were achieved. Clinical abdominal dehiscence is rarely immediate and is unusual within 7 days of surgery. Its pathogenesis is multifactorial. When failures of the suture material and knots are excluded it is determined by the ability of the sutured tissue to resist tension, particularly as a consequence of abdominal distension.'As tension increases, the encircled tissues become ischaemic and the suture cuts through in a progressive fashion. Niggebrugge *et al.* propose that, because their double-loop closure will tighten as abdominal pressure increases, this will be beneficial, because apposition of the wound edges will be maintained. Jenkins[1] found that, in post-surgical distension, abdominal girth might increase by up to one-third, and xipho-pubic distance by two-thirds. In a mathematical analysis of the relationship between wound and suture length he stressed the importance of a suture placement that allowed compliance of the abdominal wound and minimized increase in tension.

Statistical significance and clinical relevance can be disparate entities Animal models may be a necessity to advance medical science but in an age in which there is increasing public intolerance to animal experimentation we must ensure that, when animals are used, it is to answer the appropriate questions

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1 Jenkins TPN. The burst abdominal wound. a mechanical approach. *Br J Surg* 1976; 63: 873–6.

Thoracoscopic parathyroidectomy of an ectopic mediastinal adenoma

Sir

We read with interest the paper by Mr Gullstrand and colleagues (*Br J Surg* 1996; 83: 1757). The thoracoscopic approach was wrongly presented as a new method. During the 94th Congrès Français de Chirurgie held in Paris in 1992 we presented a videotape entitled 'Resection of a parathyroid mediastinal adenoma through a thoracoscopic approach' This was the first case of thoracoscopic parathyroidectomy of an ectopic mediastinal adenoma which was published[1] in association with one of our other patients and two others reported by Professor Richard Prinz at St Luke's Medical Center in Chicago, Illinois, USA. We are very surprised that this reference was not mentioned in the article by Gullstrand *et al.* but note with pleasure that this new approach has been developed in other institutions.

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1 Prinz R, Lonchyna V, Carnaille B, Wurtz A, Proye C. Thoracoscopic excision of enlarged mediastinal parathyroid glands *Surgery* 1994; 116: 999–1005.

Simple technique for endoscopic subfascial dissection of perforating veins

Sir

We read with interest the article by Dr Kok and colleagues (*Br J Surg* 1997; 84. 333) describing a novel method of dealing with perforating veins endoscopically using existing laparoscopic instruments and a proctoscope. One of the main advantages proposed is that this minimally invasive technique avoids a long incision through diseased skin, thereby decreasing the incidence of wound infection and skin necrosis.

The Introduction refers to the article by Linton[1] from 1938 and the authors suggest that incompetent perforating veins are a crucial factor in the pathogenesis of varicose ulceration. More recent evidence suggests that perforating vein ligation may only have a limited place in the treatment of venous ulceration[2]. The majority of venous ulcers with or without perforating vein incompetence can be healed by high tie of the long saphenous vein, stripping of the vein to the knee and multiple avulsions.

Evaluation of venous function suggests that no further haemodynamic improvement can be achieved by the addition of perforating vein surgery[3].

Perforating vein surgery will probably have a limited place in the treatment of venous ulcers and currently surgical ligation by any means cannot be recommended. Clinical trials are needed to assess the outcome of perforating vein surgery.

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1 Linton RR. The communicating veins of the lower leg and the operative technic for their ligation. *Ann Surg* 1938; 107: 582–93.
2 Ruckley CV, Makhdoomi KR The venous perforator *Br J Surg* 1966; 83 1492–3
3 Akesson H, Brudin L, Cwikel W, Ohlin P, Plate G. Does the correction of insufficient superficial and perforating veins improve function in patients with deep venous insufficiency? *Phlebology* 1990; 5. 113–23.

Removal of the anus during proctectomy

Sir
We read with interest the article by Messrs Frizelle and Pemberton (*Br J Surg* 1997, 84: 68). They discuss leaving the anal canal *in situ* following proctectomy for inflammatory bowel disease and suggest that anal excision can result in delayed healing of perineal wounds. They cite a report from Birmingham, relating delay in return to work of up to 6 months to delay in perineal wound healing[1]

Work from St Mark's Hospital[2], however, reports the results in 23 patients (19 ulcerative colitis, three Crohn's disease and one familial adenomatous polyposis) in whom the anal canal was left *in situ* following proctectomy It showed that this is associated with considerable morbidity. Uncomplicated healing occurred in only three patients and 11 patients developed anal discharge and nine infected haematomas. Fourteen patients developed pelvic sepsis and none of these healed despite surgical curettage. Eleven patients ultimately healed at a median of 28 months. Eight patients had persistent sepsis after a median of 45 months.

There might appear to be potential benefits of leaving behind the anal canal under these circumstances; for instance, patients can undergo a 'trial of ileostomy' deferring the need to decide on pouch reconstruction until a later date. Such a practice may well lead to severe postoperative morbidity and delay in return to work may be significantly longer than that experienced by delay in perineal wound healing We would counsel against such a practice in patients with inflammatory bowel disease based on this data

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1 Wyke RJ, Edwards FC, Allan RN Employment problems and prospects for patients with inflammatory bowel disease *Gut* 1988, 29. 1229–35.
2 Talbot RW, Ritchie JK, Northover JMA. Conservative proctocolectomy: a dubious option in ulcerative colitis. *Br J Surg* 1989, 76: 738–9.

Closure of loop ileostomy

Sir
We read with appreciation the Short Note on stapled side-to-side closure of loop ileostomy by Messrs Berry and Scholefield (*Br J Surg* 1997; 84: 524). We have been using this method for the past year and can confirm that gastrointestinal function returns more quickly than with a sutured, end-to-end closure.

We should like to make two points. First, care must be taken not to perforate the ileum with the tips of the stapling arms and we advocate routine air testing (with syringe and needle) on completion to check the integrity of the bowel wall and staple line. Second, at manufacturer's list prices, the GIA-80 (AutoSuture, Ascot, UK) stapler costs £179 and its refill a further £103 (the GIA-60 costs £108 and refill is £75) with VAT being extra. Use of the refill to construct a stapled-end closure costs an additional £103 or £75 (plus VAT). This may be an unnecessary extravagance, as, after the first pass of the stapler to construct the side-to-side anastomosis, the free end of the bowel can usually be closed equally well by conventional sutures.

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Adenocarcinoma arising on the site of a Gelpi retractor after coloanal anastomosis for rectal cancer

Sir
I was interested in this Case Report (*Br J Surg* 1997; 84. 362) having looked after two similar patients. I attributed them to trauma from the anaesthetic hose I was then using to evacuate the effluent of orthograde colonic lavage (used to eliminate exfoliated cells from the bowel proximal to the tumour before division above). I, thereafter, ceased on-table anal intubation.

It is intriguing, though, that any cells, viable or not, could survive to implant after povidone–iodine washout of the rectum below the lower clamp before division.

Both patients had recurrence in the dermis of the anal verge and certainly appeared implantational, macroscopically and microscopically. In a third patient eight separate nodules of tumour grew in the rectal stump after anterior resection, three at the suture line and five in the mucosa below. These were probably metastatic in origin, either lymphatic or venous. This patient also had anal intubation during surgery and perhaps this damages lymphatics and veins to allow a tumour embolus to stop and grow rather than pass onwards. All three patients developed metastases elsewhere.

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Surgical management of complicated colonic diverticulitis

Letter 1

Sir
The article by Professor Wedell and colleagues (*Br J Surg* 1997; 84: 380–3) warrants comment.

Based on a 1 per cent mortality rate for primary anastomosis *versus* seven deaths in 31 patients undergoing Hartmann's procedure, the authors claim that primary anastomosis is preferable in 'all stages of acute diverticulitis' and state that 'these data disprove any suggestion that case selection explains the poor result' from the Hartmann's procedure. Unfortunately, Wedell *et al.* fail to provide the severity of illness of their patients, measured by one of the objective physiological scores available. In addition, during the last phase of the study (1987–1995), corresponding to a greater use of primary anastomosis in patients with diffuse peritonitis (i.e. stage III disease), they treated intra-abdominal infection more aggressively using a policy of planned re-laparotomy.

I suggest therefore that without this data the results are based on a selection bias and may be meaningless

The authors state that death from 'continuing sepsis' .. 'may be a consequence of incomplete resection of the involved sigmoid mesocolon'. Do they have any evidence to offer that resecting some connective tissue, fat and blood vessel (after the source of infection has been eliminated by resecting the colon) will eliminate 'sepsis'?

In Patients and Methods they write 'In the 1980s perioperative one-shot antibiotic therapy with 4 g cefotaxime was introduced' Was one-shot cefotaxime used to treat patients with diffuse faecal peritonitis? 'One-shot prophylaxis' is a well proven policy but 'one-shot therapy' is unproven.

The authors report one 'clinical' anastomotic leak (causing death but described as 'minor') in the 148 patients undergoing primary anastomosis without a protective colostomy. To the best of my knowledge this is the lowest leakage rate ever published for patients with complicated diverticular disease. The authors should be congratulated for this achievement.

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Letter 2

Sir

I read with interest the article by Professor Wedell and colleagues, describing their experience of the surgical management of complicated colonic diverticulitis. I consider that the authors' conclusions, suggesting that a single-stage procedure was both superior to and safer than Hartmann's procedure, were not supported by the data presented. The study was retrospective and unmatched, both in sample size (148 single-stage procedure *versus* 31 Hartmann's procedure) and case mix (25 per cent emergency *versus* 75 per cent elective). The proportion of emergency patients undergoing Hartmann's procedure is not mentioned in the report, but six of the seven patients who died following this procedure had perforated diverticular disease with generalized peritonitis and other significant illnesses.

Most of the deaths were in the group that presented as an emergency but, importantly, the physiological status of the patients was not mentioned. It is probable that this group of patients were sicker than the elective group and this could account for the apparent worse outcome

Another point raised in the report was that only 31 per cent of patients undergoing Hartmann's procedure were reversed and 50 per cent either died, had carcinomatosis or another disease process making reversal very unlikely.

The observational study does show that excellent results can be achieved using a single-stage procedure, but the study design is inadequate when it comes to deciding which procedure is safest, particularly in the emergency situation I think that contrary to the authors' conclusions it is very likely that illness severity decided outcome rather than the type of surgery employed.

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Letter 3

Sir

Professor Wedell and colleagues are to be congratulated on their excellent results in the management of complicated colonic diverticulitis. We entirely agree that there are no longer any clinical indications for the three-stage operation, even in an emergency situation. We also agree that resection with primary anastomosis is probably the best procedure in stage I and II of complicated diverticulitis in an elective situation.

There are, however, not enough arguments to state that this goes for stage III as well. Hartmann's resection was done mainly in stage III patients (15 of 31). It is not entirely clear which type of operation was performed in the 56 patients undergoing emergency surgery. If we compare *Table 1* (preoperative diagnosis and intraoperative findings in 56 emergency patients) and *Table 2* (indication for Hartmann's procedure) we assume that all 31 Hartmann's procedures were carried out as emergency operations. It would be interesting to know the Acute Physiology And Chronic Health Evaluation (APACHE) II score of these 56 patients who had emergency surgery and to reassess the operative results in view of these results Eleven of 13 patients who died following surgery had emergency surgery Eight of these patients had stage III disease, three had stage II disease. It seems that whether or not a patient requires emergency surgery is the most important predictive factor of mortality. The classification the authors use does not take into account the concomitant diseases and the physiological state of the patient at the time of operation This must have had an influence on the decision of whether to carry out a primary anastomosis or a Hartmann's resection

Based on the data presented in their study we cannot agree with the statement that resection with primary anastomosis is the safest procedure for *all* stages of complicated diverticulitis.

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Author's reply

Sir

I was pleased in the interest generated by our paper and can understand critical comments about the retrospective review.

Krukowski and Matheson showed, however, that patients with generalized or faecal peritonitis secondary to diverticulitis are uncommon and the experience of individual surgeons varies from three patients in 9 years to 23 patients in 15 years[1] This emphasizes the difficulties of mounting appropriate studies in this condition.

The Lahey Clinic in a study conducted between 1967 and 1982 reported a 1 per cent mortality rate of primary anastomosis and 16 per cent mortality rate of two-stage operations with a conclusion that resection with primary anastomosis may be a suitable option in managing patients with generalized peritoneal contamination[2].

Mr Richards mentioned the ratio of 25 per cent emergency *versus* 75 per cent elective operations. This figure represents evidence for unequivocal generalized peritoneal contamination or a progression of localized peritonitis despite adequate antibiotic therapy. Not every diagnosis of pelvic peritonitis is an indication for emergency surgery.

Mr Willemsen and Mr Richards: 25 of 33 patients with perforated diverticulitis and purulent or faecal peritonitis (stage III) underwent emergency surgery. Fourteen patients had resection with primary anastomosis, nine patients had a Hartmann's procedure and two patients a staged resection. Seven patients died, one patient after resection and primary anastomosis, four patients after Hartmann's procedure and two patients after staged resection.

It is our experience that there is no difference between resection with primary anastomosis and Hartmann's operation (provided the same criteria of complete resection of the sigmoid and mesosigmoid colon are followed) in relation to the duration of the operative procedure or the operative stress for the patient. The indication for Hartmann's operation or resection with primary anastomosis is not based on the stage of the patient's illness but more on the presence or absence of concomitant disease. The procedure is also determined by intraoperative findings and the technical possibilities (*Table 2*).

Mr Richards raises the point that it is usually the complicated diverticulitis that kills the patient and not the surgeon and in this circumstance resection with primary anastomosis would not change the outcome. A cost-sparing one-stage operation should be favoured avoiding a possible life-long colostomy especially in elderly patients.

Mr Schein: Continuing pelvic sepsis, often followed by rectal stump leakage or breakdown, is usually a problem of inadequate resection, particularly at the distal margin leaving *in situ* active disease as unsuspected colovaginal fistulas or pericolic and rectal and intramural abscesses. Death in seven of the 13 patients was judged to have resulted from these complications. As Berry *et al.*[3], we consider continuing sepsis as the source of a higher mortality and morbidity rate. As total excision of the mesorectum helps reduce local recurrence in rectal cancer, so total excision of the mesosigmoid reduces chances of continuing pelvic sepsis.

Mr Schein: In the 1980s a perioperative one-shot single-dose prophylaxis with 4 g cefotaxime was introduced for all patients undergoing colonic surgery. This therapy was modified according to results from intraoperative microbiological studies or from material after computed tomography-guided abscess puncture or drainage in patients with diffuse or localized peritonitis.

Fifteen years have passed since the Lahey Clinic review and by using different new techniques there is a possibility of making primary anastomosis after resection safer. Better control of peritoneal sepsis may reduce mortality rates.

In conclusion:

> Not the experience of one man only or of one generation, but the accumulative experience of all mankind in all ages.
>
> *F. W. Herschel* (1738–1822)

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1 Krukowski ZH, Matheson NA. Emergency surgery for diverticular disease complicated by generalized peritonitis: a review *Br J Surg* 1984; 71: 921–7.
2 Hackford AW, Schoetz DJ Jr, Coller JA, Veidenheimer MC. Surgical management of complicated diverticulitis: the Lahey Clinic experience, 1967–1982. *Dis Colon Rectum* 1985; 28: 317–21.
3 Berry AR, Turner WH, Mortensen NJ, Kettlewell MG. Emergency surgery for complicated diverticular disease. A five-year experience. *Dis Colon Rectum* 1989; 32: 849–54.

Prospective audit of surgery for varicose veins

Sir

We read with great interest the paper by Mr Lees and colleagues (*Br J Surg* 1997; 84: 44–6). We were impressed by their honest reporting of an acknowledged problem but are surprised that they are unaware of the solution.

They refer to the need to continue the study 'with a greater number of surgeons and hospitals'. The problem, however, was encapsulated in a *British Journal of Surgery* Leading Article[1] and quoted by the authors Within the article is a vignette in which a trainee admitted lack of confidence about operating on a patient with varicose veins. The consultant insisted that the trainee carry on, unsupervised, because he had a management meeting to attend. In Mr Lees' series of 33 patients (50 limbs) the most senior operating surgeon present was the consultant for only 16 of the 50 legs. Preoperative duplex scanning would do nothing to improve the standard of operative surgery, as the authors have demonstrated, as an incorrect preoperative diagnosis was the cause of failure in only one limb. Inadequate surgery was the cause of failure in all but two of 15 limbs with persisting incompetence.

In a review of 599 patients (973 limbs)[2], of whom 17 per cent were recurrent, the consultant surgeon was present at 92 per cent of operations (this series includes private patients so the proportion reduces to 86 per cent for National Health Service operations). We reviewed a complete series of operations on 295 limbs with recurrent varicose veins Thirty-six of these were in-house recurrences generated over approximately 11 years and in these the problem of inadequate saphenofemoral ligation occurred only three times. Two locum consultants operated on two of the patients, while the consultant in charge was responsible for the third. There was no case in which a trainee, either supervised or unsupervised, was responsible for inadequate saphenofemoral ligation.

Many previous publications have demonstrated inadequate training leading to inadequate surgery. The task is to teach trainees how to carry out accurate saphenofemoral ligation and to strip the long saphenous vein and, at a later stage, progress to saphenopopliteal ligation and operations for recurrence. There have been substantial improvements in surgical training in this country in recent years and there is no reason why trainees should not master these techniques.

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1 Negus D. Recurrent varicose veins: a national problem. *Br J Surg* 1993; 80: 823–4.
2 Critchley G, Handa A, Maw A, Harvey A, Harvey MR, Corbett CRR. Complications of varicose vein surgery. *Ann R Coll Surg Engl* 1997; 79: 105–10.

Authors' reply

Sir

We thank Messrs Handa, Maw and Corbett for their interest in our paper. They feel that we are unaware of the solution to the problem of inadequate surgery that we highlighted. We would agree with them, and that the paper illustrates a need to provide better training and supervision of trainees, and this was stated and discussed in the penultimate paragraph of the discussion. We are therefore well aware of this solution.

Based on our study we now provide a consultant-based service for varicose vein surgery with a high level of consultant supervision and training of juniors. It will require continuation of the study with completion of the audit cycle to ascertain whether this improves results.

The authors suggest that meticulous operative technique alone will prevent varicose vein recurrence and reference an interesting retrospective paper. This publication, however, does not indicate the number of patients undergoing varicose vein surgery during the period of the study, nor does it identify recurrence rates. It is not possible to conclude that trainees are not responsible for any inadequate surgery.

We suggest that, in addition to meticulous surgery, accurate preoperative assessment is of benefit in preventing recurrence. A recently performed study shows that clinical assessment has an inaccuracy rate of 20 per cent and with the addition of a hand-held Doppler device, 13 per cent of limbs were still assessed inaccurately[1].

Accurate preoperative assessment and meticulous surgery are both important factors in reducing recurrence rates following varicose vein surgery.

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British Journal of Surgery 1997, 84, 1180–1181

Book reviews

Cardiac Surgery. Safeguards and Pitfalls in Operative Technique. 2nd ed.

S. Khonsari (ed.). 285 × 222 mm. Pp. 341. Illustrated. 1996. Philadelphia, Pennsylvania: Lippincott–Raven. £149.50.

This is the second edition of a book that is essentially an atlas with excellent text covering the whole spectrum of cardiac surgery. The high points are the clear diagrams and the detailed discussion of common problems. The move from an apprenticeship to a shorter residency-type training, which Calman changes have produced in the UK, has increased the need for a volume of this kind that will serve as an excellent introductory guide to individuals in cardiac surgery in their first few years. The book presents a North American view of cardiac surgery that is somewhat different from European views; for example, it does not cover non-cardioplegic methods of myocardial protection for coronary artery surgery. The early chapters deal with the essence of cardiopulmonary bypass and details of cannulation technique. There is a short chapter on myocardial protection and a chapter that deals with venting and de-airing, an important subject often left undiscussed. Further text deals with all types of adult and congenital heart disease. There are particularly clear drawings of the relationships of the aortic valve and the mitral valve, and precise details are given of correct suture placement for valve insertion. The chapter on surgery of the aorta is good overall, with details of how to handle complications. It is peculiar that the Marfan-type aorta is omitted, especially in view of the increasing tendency towards early prophylactic surgery for this condition in order to stabilize the aortic root. The intricacies of perfusion techniques for surgery of the aorta are not dealt with in detail, although there is some discussion of retrograde cerebral perfusion. The section on congenital heart disease contains some excellent illustrations, and very clear diagrams are given to enhance the discussion of anomalous pulmonary venous connection and atrioventricular septal defect in particular. There are clear descriptions of right atrial and right ventricular anatomy. In summary, this is a book to be recommended, especially to specialist registrars in cardiac surgery. A trainee who reads the description of an operation on the preceding evening would be well placed to understand the procedure in greater depth the following day.

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Emergency Vascular Practice

A. D. B. Chant and A. A. B. Barros D'Sa (eds). 279 × 203 mm. Pp. 269. Illustrated. 1996. London: Arnold. £95.

Emergency and urgent work comprise a sizeable proportion of a vascular surgeon's workload, so the subject addressed by this new book is an important one. Collecting material on this topic together in a single volume has been a helpful venture, as it would otherwise need to be searched out in periodicals and in the larger general textbooks of vascular surgery. The coverage is comprehensive. There is an informative chapter dealing with cold injury, and acute deep vein thrombosis of the upper extremity is very well reviewed. The absence of a chapter on the aneurysmal and thrombotic complications of drug abuse might, however, be considered an omission. Many of the chapters are set out in a structured way and adopt a 'how I do it' approach. This inevitably leads to controversial advice in some cases but the sections on the control of perioperative bleeding problems, and urgent and emergency aortic aneurysm are worthwhile reading for vascular trainees. Vascular trauma, particularly penetrating injury, is given extensive coverage and occupies about 30 per cent of the volume. This book would, therefore, be of interest to trauma as well as vascular surgeons.

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Medicolegal Reporting in Surgery

B. J. Jones (ed.). 240 × 160 mm. Pp. 314. Illustrated. 1996. Edinburgh: Churchill Livingstone. £55.

This is not an easy book on which to pass comment. For a start the title is misleading as the book deals only with trauma. Of the 12 chapters, ten are very competent and copiously referenced summaries of the effects and management of non-orthopaedic trauma affecting different parts of the body. There is in addition a sensible chapter on chronic pain and a sound introduction to the legal side of medicolegal work. One is, however, left wondering at whom the book is directed. For experts in the specific areas the summaries might be useful and the references particularly valuable, but the text is surely too technical for what the jacket refers to as 'legal and insurance personnel'. One is thus left with the uncomfortable feeling that the main beneficiary may be that jack of all trades, the professional medicolegal opinion, a breed we are asked to hope will soon be extinct. In the meantime this book will be godsend for them.

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Cambridge Textbook of Accident and Emergency Medicine

D. Skinner, A. Swain, R. Peyton and C. Robertson (eds). 282 × 222 mm. Pp. 1269. Illustrated. 1997. Cambridge: Cambridge University Press. £120.

The timely arrival of a big red book to replace the blue one is a political coincidence. The publication of a major British reference textbook on accident and emergency (A and E) medicine is in line with the academic development of the specialty, covers the subject in greater breadth and depth compared with Rutherford's texts of the 1980s, and is much more extensively referenced. Its large authorship includes experts in many areas of A and E medicine from home and abroad. Text by A and E specialists, on wounds, spinal injury, electrical injuries and death, is full of interesting practical advice and common sense. Contributions from other specialists provide a variety of style, insight and emphasis. With 63 chapters and 110 authors, the editors can be congratulated for producing a cohesive publication with few errors or contradictions. The quality of some radiographs and photographs, and the absence of colour, detract from clarity but at £120 it is good value. This Cambridge book has much to interest surgical trainees who will find it a useful source of advice and education; it should be on hand for use by all A and E medical and nursing staff on a 24-h basis.

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Surgery of Infants and Children. Scientific Principles and Practice

K. T. Oldham, P. M. Colombani and R. P. Foglia (eds). 285 × 220 mm. Pp 1834. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott–Raven. £191.75.

This is a magnum opus and, without doubt, the most authoritative and up-to-date reference book currently available in the field. It draws on the considerable experience of 149 contributors working at centres of excellence, predominantly in North America, in addition to senior professionals of international repute. The three editors have recruited many authors who are young and actively engaged in basic scientific research related to the whole spectrum of paediatric surgical care. There is a freshness and immediacy to the text which is generously complemented by outstanding line drawings as well as good-quality computed tomograms and clinical photographs. The decision, however, to include seven pages of expensive colour figures at the beginning of the book, disassociated from their individual places in the text, is unhelpful. At a cost of £192 few paediatric surgeons will be able to afford to purchase this book for their personal use, but it should be made available in most departmental libraries where it will be a source of inspiration and deeper understanding of one of the most exciting and rapidly advancing surgical specialties. The editors have undoubtedly succeeded in their goal to provide just this.

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British Journal of Surgery 1997, **84**, 1182

Notices and announcements

31 August–3 September 1997
19th ESPEN Congress on Clinical Nutrition and Metabolism
Amsterdam, The Netherlands
Information Van Namen and Westerlaken Congress Organisation Services, PO Box 1558, 6501 BN Nijmegen, The Netherlands

4 September 1997
Total Mesorectal Excision Study Day
Sheffield, UK
Information: C. Stenton, Short Course Officer, Faculty of Medicine, The Medical School, Sheffield S10 2RX, UK

7–12 September 1997
8th International Congress on Cleft Palate and Related Craniofacial Anomalies
Singapore
Information: Dr L. Keuk, Organising Committee, Academy of Medicine, 16 College Road, Singapore 0316

12–17 October 1997
Management of Emergencies and Disasters: A Multidisciplinary Approach
Stoke, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

12–18 October 1997
Telemedicine and Telecare
Belfast, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

15–22 October 1997
Cancer in Children: Challenges and Controversies
London, UK
Information Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

23–24 October 1997
2nd Nottingham International Colorectal Cancer Symposium
Nottingham, UK
Information: J. D. Hardcastle, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

6–19 November 1997
Hong Kong International Cancer Conference and Asian Pacific Cancer Congress 1997
Hong Kong
Information. Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

27–28 November 1997
31st Meeting of the Vascular Surgical Society of Great Britain and Ireland
London, UK
Information: T Szymanska, Vascular Surgical Society of Great Britain and Ireland, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information. M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information: O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

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Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
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Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer
Terme di Valdieri, Italy
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Leading articles

Neoadjuvant therapy for oesophageal cancer

The term neoadjuvant is used differently by different authors, although it seems generally to mean some form of preoperative therapy. Some authors use the term for preoperative radiotherapy and others for preoperative chemotherapy but, although both may be adjuvant, neither of these treatments is new. Therefore, if neoadjuvant is to be used as a term with a different meaning from preoperative, it is probably best confined to what is a relatively new approach: preoperative chemotherapy and radiotherapy given together. That is how the term is used in this leading article.

Some 30 years ago, any review of oesophageal cancer would have addressed squamous cell carcinoma of the oesophagus almost exclusively. Today, in countries such as Japan and China, a preponderance of this disease remains the case. In the English-speaking world and the rest of Europe, however, adenocarcinoma involving the lower oesophagus now accounts for approximately half the cases of oesophageal cancer that are being treated. It has usually been accepted that adenocarcinoma of the oesophagus carries a poorer prognosis than squamous carcinoma (which is bad enough anyway) so that this increased incidence of adenocarcinoma might be expected to make the outlook for patients with cancer of the oesophagus even worse than it has been previously.

In relatively large series from centres with expertise in the treatment of oesophageal cancer and where some form of patient selection is almost inevitably applied (or imposed by the referral pattern), overall survival rates are not too dissimilar, regardless of the type of surgical treatment undertaken. Even in such highly selected series the 5-year survival rate is only of the order of 25–30 per cent, and in many series where patient selection is less and yearly operative numbers are smaller, the 5-year survival rate is worse. Furthermore, attempts to improve on surgery, either by preoperative or postoperative radiotherapy, by preoperative or postoperative chemotherapy, or by treating oesophageal cancer by either modality alone, have not offered a better outlook[1].

A review of results at the Royal Adelaide Hospital was undertaken in 1984; the 5-year survival rate of patients treated surgically was approximately 5 per cent and that for those treated by radical radiotherapy alone was 4 per cent. These values are similar to those published by Earlam and Cunha-Melo[2] in 1980 in their extensive review of the world literature in which they came up with rates of 5 and 5 per cent respectively. It was therefore with considerable interest that we read the article by Leichman *et al.*[3] in 1984 and the accompanying editorial in the *Journal of Clinical Oncology* on the use of radiotherapy and chemotherapy concomitantly, as preoperative adjuvant therapy to surgery. The theoretical reasons for using such therapy may be summarized as follows. First, there is independent activity of each treatment mode, i.e. radiotherapy for the primary site and chemotherapy for both the primary site and also micrometastatic disease. As the toxicity of each mode tends to be different, there is a summation of tumour activity without summation of toxic effects. Second, there may be a synergistic effect with the total summation being greater than that expected from a simple addition of individual effects. This may be related to chemotherapy making the tumour more sensitive to radiotherapy, or vice versa or, perhaps, both[4].

Following the lead of Leichman *et al.*, we embraced the concept of neoadjuvant therapy for oesophageal cancer and have progressively published our results[5–8]. In brief, it was found that the survival rate for unselected patients has improved markedly to approximately 23 per cent at 5 years, that neoadjuvant therapy produces a similar disappearance of tumour for both adenocarcinoma and squamous cell carcinoma, and that complete disappearance of tumour in the resected specimen occurs in about 20 per cent of cases, a feature that is associated with a survival rate of approximately 67 per cent at 5 years. Over the same time period other authors have also followed the lead of Leichman and colleagues, with the result that about two-thirds of published trials have found that neoadjuvant therapy produces a survival advantage compared with controls.

It is difficult to compare the data from various groups because of differences in drug protocols and criteria for assessing complete response. Furthermore, preoperative staging has been variable. Most trials have used combinations of 5-fluorouracil and cisplatin, although there is no agreement on the combination, dosage and duration of therapy. Like us, some workers have found that survival is increased greatly for patients who have a complete histological response[9,10]. Perhaps the most important paper published to date is that of Walsh *et al.*[10], which describes for the first time a controlled and randomized study demonstrating a survival advantage in a group of patients with adenocarcinoma of the oesophagus treated with neoadjuvant therapy and surgery, compared with a group treated by surgery alone.

Further similar studies are needed, as are trials to determine whether radiotherapy and chemotherapy given synchronously without surgery is an appropriate treatment for some patients. From a surgical standpoint, ever wider node resections have not been proven to produce better results, although Japanese surgeons in particular argue strongly for such an approach. In general, however, techniques such as three-field lymph node resection have not found favour in the West.

Neoadjuvant therapy for oesophageal cancer had a rather slow start but is now widely used and scientific evidence for its benefit is slowly emerging. Nevertheless, when used for other cancers results have been mixed[4] and it seems prudent to advocate it with caution. Surgical resection remains the 'gold standard' of treatment for oesophageal cancer because it addresses the mechanical problems and is sometimes associated with cure. However, radiotherapy plus chemotherapy,, used before operation, has been the only bright star to have emerged in the treatment of this disease in the past 15 years.

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Atherosclerotic renal artery stenosis

Atherosclerotic renal artery stenosis (RAS) has become recognized as a major cause of renal disease in the elderly. In selected patients excellent results may be obtained by operation to improve renal function; the extreme example of this is in dialysis-dependent patients who may regain renal function after renal artery surgery or angioplasty[1]. Any risk of surgery[1] must be weighed against the very poor prognosis of patients with atherosclerotic RAS on haemodialysis. Over 50 per cent of such patients will die within the first 2 years of starting dialysis[2]; a recent study from Aberdeen paints an even bleaker picture[3]. RAS without severe renal impairment or hypertension is common in patients having angiography for peripheral arterial disease. Although estimates vary, probably between 40 and 50 per cent of such patients have stenosis. In a study of 1302 individuals undergoing coronary angiography, 30 per cent were found to have atherosclerotic RAS and the presence of peripheral vascular disease was one of the most powerful predictive factors for such stenosis[4]; in keeping with other data, the presence of hypertension was not associated significantly with renal artery narrowing. Such reports confirm the common association of RAS with peripheral arterial disease.

Historically, an arterial stenosis causing a reduction of less than 50 per cent in diameter has not been considered haemodynamically significant. Although true with regard to renal blood flow at a point in time, it is certainly not true of the future and it belies the importance of the lesion to the patient. Recent studies using duplex ultrasonography have shown that stenotic disease progresses, and that more severe grades of stenosis will progress to occlusion[5]. This is in keeping with early animal work which showed that although blood flow in the femoral artery is not decreased with stenosis up to 70 per cent in area, above this level there is a catastrophic decline in flow. One must remember that the gradual occlusion of atherosclerotic RAS is usually an asymptomatic process unless it affects a single kidney. Strandness's group have shown that a 60 per cent or greater stenosis detected by duplex scanning has a 5 per cent chance at 1 year and a 10 per cent chance at 2 years of progression to occlusion[5]. They have also shown that when there is a stenosis of 60 per cent or greater 19 per cent of kidneys will have lost 1 cm or more in length by 1 year[6]. This is secondary to a decrease in renal parenchyma, with the irreversible replacement of glomeruli and tubules with fibrous tissue[7]. The frequent use of angiotensin converting enzyme inhibitors in patients with peripheral arterial disease has become recognized as a major problem in those with occult RAS. Kidneys with degrees of arterial stenosis which do not affect renal function may suffer a decline in function with time when these agents are prescribed and this can lead to acute renal failure. It is important to realize that, for older patients, a plasma creatinine level of 200 μmol/l may represent a loss in overall renal function of 50 per cent in men and 66 per cent in women.

Atherosclerotic RAS is also a marker for atheroembolic disease. If atheroembolic disease is identified on renal biopsy, there is an 80 per cent chance of arterial stenosis affecting that kidney. Atheroembolic disease has been recognized as an important problem by vascular surgeons for many years, but has only recently become recognized as an important cause of renal disease in the elderly[8]. It can be precipitated by angiography, anticoagulation or thrombolysis, which are all relatively common treatment options that may be contemplated in patients with peripheral arterial disease and occult RAS.

The finding of high-grade bilateral RAS, or occlusion with a contralateral high-grade stenosis, may make revascularization of the renal tissue a higher priority than intervention for peripheral arterial disease. One study has shown that the initial angiographic appearance of the renal arteries determines the prognosis of both patient and kidney[9]. Those who present with occlusion on one side and occlusion or stenosis on the opposite side have a mortality rate of greater than 50 per cent at 2 years. This may seem to be an uncommon situation, but Connolly *et al.* found this combination in approximately one-third of patients presenting to a renal unit with atherosclerotic RAS. So angiography of the renal arteries can give the vascular surgeon some understanding of the long-term prognosis of the patient with peripheral arterial disease. Missouris *et al.*[10] reported that, if RAS was identified at angiography for peripheral arterial disease, the mortality rate for patients having surgery for such disease was 32 per cent, compared with 0 per cent in those who did not have RAS. The survival rate in patients found at coronary angiography to have RAS was 65 per cent at 4 years compared with 86 per cent in those without RAS[11]. These data confirm the clinical impression of many vascular surgeons that such patients are high-risk cases.

The value of simultaneous aortic and renal artery reconstruction is controversial. Recent publications suggest that this can be performed with mortality and morbidity rates similar to those of aortic reconstruction alone[12]. However, one randomized controlled trial comparing percutaneous transluminal renal angioplasty with surgery recommended that angioplasty should be the first choice, even though the results of surgery were slightly better[13].

Imaging of the renal arteries should be performed in any angiographic study undertaken for peripheral arterial disease. In future, non-invasive techniques may be available that can reliably diagnose RAS but, at present, intra-arterial digital subtraction angiography remains the best investigation. The angiographic appearance of the renal arteries may alter the immediate management of the individual patient. Patients with atherosclerotic RAS need careful nephrological follow-up with respect to renal dysfunction and troublesome hypertension due to progressive stenosis, irrespective of any surgical action. Atheromatous RAS is important for the vascular surgeon, nephrologist and, not least, the patient.

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Review

Helicobacter pylori and gastric cancer

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Background Considerable progress has been made over the past two decades in understanding gastric carcinogenesis. Genetic and environmental factors have been shown to play a part. Infection with *Helicobacter pylori* leads to chronic gastritis and evidence is accumulating to link this disease with the subsequent development of gastric cancer.
Method A literature review was undertaken using Medline (National Library of Medicine, Washington DC, USA) searches of the headings gastrointestinal neoplasms and *H. pylori* for the years 1993–1997; further relevant references were examined.
Results *H. pylori* is implicated in gastric carcinogenesis. Proposed mechanisms centre on the inflammatory response of the gastric mucosa to the bacterium.
Conclusion Investigation is still required to elucidate the exact role of *H. pylori* in the development of gastric carcinoma. Eradication of the organism in high-risk groups might lead to a reduction in the incidence of gastric cancer.

Despite falling rates of gastric cancer in the West[1], this tumour remains one of the most common neoplasms in many parts of the world, including Japan, Latin America and much of Asia[2]. In a worldwide context, it is a disease of the poor, affecting not only less developed countries but also low socioeconomic groups within richer industrialized nations[3]. The male:female ratio of incidence is usually in the region of 2:1, although this difference is much less pronounced in younger people[1]. Certain ethnic groups within low-risk areas may show increased risk of cancer[4]. Migrant studies show that individuals acquire a higher risk of gastric cancer at an early age[5,6].

For epidemiological study, the most generally used classification of gastric cancer is that proposed by Laurén[7], which allows most cancers to be classified as intestinal or diffuse, based on their histological appearance. Intestinal-type cancer tends to occur in the gastric antrum and is the type which predominates in areas of the world with a high incidence of gastric carcinoma[8]. The diffuse type is usually found nearer the fundus, occasionally occurs in young people and is associated with blood group A[4].

Inflammation and atrophy of the mucosa is accepted by most researchers as an important prelude to the development of gastric cancer. Over the past 45 years there has been a number of systems used for classifying histological gastritis, including those proposed by Strickland and Mackay in 1973[9], Correa in 1980[10], Wyatt and Dixon in 1988[11], and Stolte and Heilmann in 1989[12]. These different systems developed as researchers began to attach aetiological significance to the different patterns of gastritis that were being recognized. Clearly there was a need for a consensus review. This was largely achieved by an advisory group to the World Congress of Gastroenterology, held in Sydney in 1990, and led to the Sydney System[13]. The System aims to include all forms of gastritis and name each type by an optional prefix denoting possible aetiology, a core description based on topography and a suffix which allocates an overall severity grading[14]. Thus advanced 'autoimmune chronic gastritis' (type A using most of the previous systems) becomes 'autoimmune-associated chronic gastritis of the corpus with severe atrophy', while 'environmental chronic gastritis' (called type B by some[11] and AB by others[12]) might be labelled '*Helicobacter pylori*-associated chronic pangastritis with moderate atrophy'.

A system for classifying the endoscopic appearance of gastritis and duodenitis was devised by the same advisory group[15]. A number of categories were defined, including 'endoscopic erythematous/exudative gastritis', 'flat erosive gastritis', 'raised erosive gastritis' and 'endoscopic atrophic gastritis'. These categories have not been found to correlate well with histology[16], although the endoscopic pattern of gastritis almost invariably associated with established *H. pylori* infection in Kenya can be readily identified.

Perhaps the most widely accepted sequence for the development of intestinal-type gastric cancer was proposed a number of years ago by Correa[10]. He suggested that acute gastritis progresses to a chronic stage, with atrophy of the mucosa due to loss of gastric glands. Some areas of atrophic gastritis then change to intestinal metaplasia[17]. In a number of individuals the condition progresses to dysplasia and carcinoma. This hypothesis has been supported (a) by studies of a family with a genetic predisposition to gastric cancer[18], (b) by long-term follow-up and population sample studies in Finland[19,20], and (c) by cross-sectional studies in patients with gastric cancer[21–24]. Further evidence has accumulated as intestinal metaplasia has been linked with intestinal-type gastric cancer, particularly a metaplasia subgroup designated IIB or III, secreting colonic type sulphomucins[25,26].

A number of environmental agents have been identified which may have a role in inducing gastric cancer. The most significant ones are *N*-nitroso compounds, which are known to be strong carcinogens and are formed in the stomach from nitrites[27]. A small proportion of intragastric nitrite comes from direct ingestion but most is derived from dietary nitrate (*Fig. 1*). Formation of *N*-nitroso

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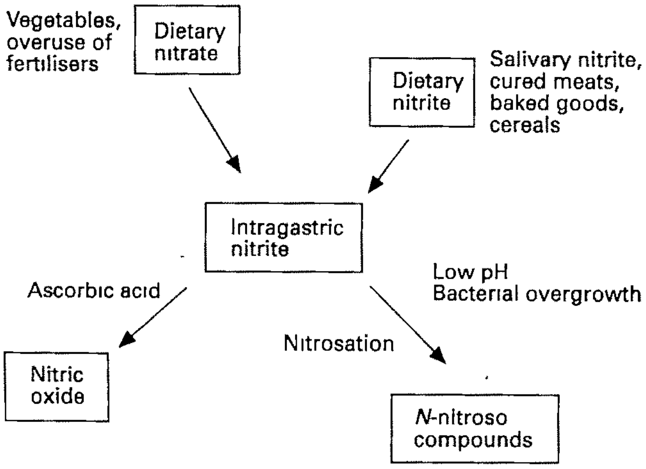

Fig. 1 Production of *N*-nitroso compounds in the stomach

compounds from intragastric nitrite usually requires an acid environment but the reaction is facilitated by bacterial overgrowth at a higher pH[28]. Vitamin C has an important defensive role, preventing nitrosation by reducing nitrite to nitric oxide. Unlike other reducing agents, vitamin C is able to catalyse this reaction in the achlorhydric stomach[29]. Evidence supporting this protective role for vitamin C in the development of gastric cancer includes (a) dietary surveys in high-risk populations showing the consumption of raw vegetables to be protective[30,31], (b) measurement of gastric ascorbic acid showing reduced levels in a population at high risk for gastric cancer compared with controls[32], and (c) studies in individuals with atrophic gastritis and intestinal metaplasia in whom levels of ascorbic acid in the stomach are decreased[33,34]. Other risk factors for the development of gastric cancer include increased salt intake[30,31,35,36], and increased starch[31] and carbohydrate[37] in the diet; selenium, beta-carotene[36] and fibre[37] may be protective.

Helicobacter pylori

In 1893, Bizzozero gave a clear description of spiral bacteria in the gastric mucosa of dogs[38]. Although this may not have been the earliest report[39], several others followed rapidly[40]. His article was followed by other reports over the next 30 years[39,40]. It is interesting to note that in 1906 the first report of spirochaetes on the surface of human gastric mucosa was in histological slides of a gastric carcinoma[41]. Despite this early research, it was not until 1983 that Warren[42] and Marshall[43] pointed out the potential importance of what they described at that time as 'S-shaped spiral bacteria'. They could be found in any part of the stomach, but most commonly in the antrum, and their presence was almost always associated with inflammation near the surface epithelium. In the following year the same authors reported that these *Campylobacter*-like bacteria could be found in the antrum of almost all patients with active chronic gastritis, duodenal ulcer or gastric ulcer[44]. Marshall, in his original letter of 1983[43], had suggested a possible link with gastric cancer but it was not until the late 1980s that papers investigating this link began to appear[45–47]. Although related to the genus *Campylobacter*, as well as to the genus *Wolinella*, closer study showed that *C. pylori* possessed a number of chemotaxonomic properties of its own and eventually it became known as *H. pylori*[48].

Epidemiology of *Helicobacter pylori*

Combining the results of serological studies from 11 developed countries reveals that between 15 and 54 per cent of the population are infected with *H. pylori*[49]. Below the age of 20 years, the prevalence of the infection is usually less than 20 per cent but it gradually increases to the age of 40 years when it levels off at around 45 per cent[49]. The most widely accepted explanation[50–53] for this pattern is based on the assumption that infection by *H. pylori* is usually acquired at an early age and is life long. The chance of an individual becoming infected has been declining during the past 50 years because of an improvement in living standards. Thus a higher proportion of a group of 15 year olds would have been infected 20 years ago than a similar group (or cohort) of 15 year olds today. The age-specific prevalence rate will therefore increase with age until the fourth or fifth decade of life. This is described as a cohort phenomenon[49].

By contrast, infection rates in developing countries are around 70 per cent in Asia[54–56] and South America[57], and between 69 and 85 per cent in Africa[55,58,59]. Infection with *H pylori* in these countries starts at an early age and is constant during adulthood[55]. It is most often acquired in the first 10 years of life, with one study from Africa showing 57 per cent of a small group of children aged between 6 months and 2 years having antibodies[59]. In a small survey of children admitted to Chogoria Hospital, Kenya, 20 per cent of the under-5-year-old age group were infected, rising to 40 per cent of 10–14-year-old children (G. Lachlan, unpublished results).

Studies in the West and in developing countries both show prevalence to be inversely related to indicators of socioeconomic status[49,56,60,61]. Sex ratios are approximately 1:1[55,62]. Although the actual mode of transmission is unknown, current evidence suggests close person to person contact in early life is important[54,63,64] and the faecal–oral or oral–oral route is likely[65].

Helicobacter pylori and gastritis

H. pylori is now recognized as the major cause of chronic superficial gastritis[19]. Marshall[66] demonstrated that gastritis follows ingestion of *H. pylori* by voluntarily swallowing a generous dose of the organism himself. Others have found that immunological and histological evidence of infection with *H. pylori* is higher in those with gastritis than in controls[45,47,67], that a positive correlation exists between the number of organisms present in the gastric mucosa and the severity of neutrophil infiltration[68], and that eradication of *H. pylori* leads to improvement in histological gastritis[69].

Once ingested, *H. pylori* tends to settle in the antral region of the stomach, but may also be seen in the body and cardia. Detailed examination of the affected mucosa reveals the surface and foveolar regions of gastric epithelium to be most often infected with the curved or S shaped bacterium, usually seen in large numbers and often in relation to intercellular junctions[70].

In the early stages of infection, this causes a marked neutrophil polymorph infiltration of the mucosa with exudate on the surface[70]. Subsequently, alignment of mucosal cells becomes uneven with loss of mucus content[71]. Chronic infection is characterized by an increase in lymphocytes and plasma cells in the lamina propria[14], with maximal activity of polymorphs centred on the pit–isthmus region[72]. This histological pattern of

Fig. 2 Histology of normal gastric body mucosa (Haematoxylin and eosin stain, original magnification × 12)

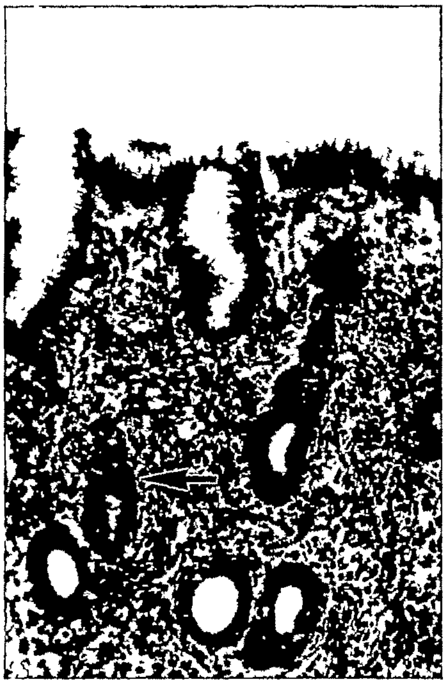

Fig. 3 Histology of chronic active gastritis of the antrum Plasma cells, lymphocytes and histiocytes are present in the superficial part of the mucosa; neutrophils within the deeper crypt epithelium (arrow) denote active gastritis. (Haematoxylin and eosin stain, original magnification × 64)

gastritis (*Figs 2* and *3*) will most often be seen in the antrum (*H. pylori*-associated chronic gastritis of the antrum) but may involve the whole stomach (when it is described as a pangastritis according to the Sydney System), a pattern more commonly seen in developing countries[10].

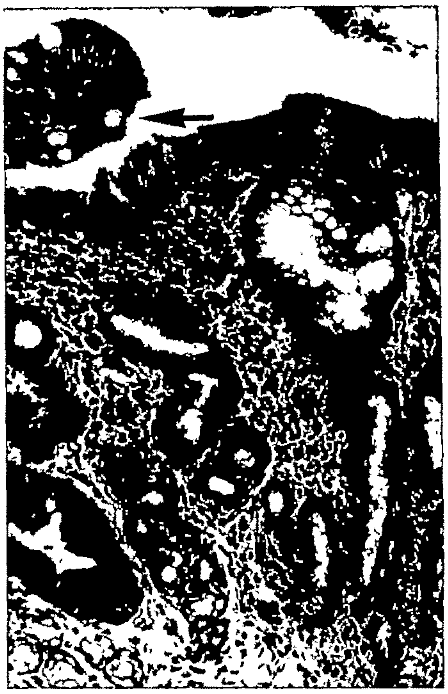

Fig. 4 Histology of gastric antrum with atrophy and intestinal metaplasia. Atrophy is recognized by the reduction of the deeper glandular component of the mucosa with the gastric foveolar (pit) region extending virtually to the muscularis mucosae Intestinal metaplasia is recognizable by the presence of goblet cells (arrow) between absorptive cells. (Haematoxylin and eosin stain, original magnification × 32)

The role of *H. pylori* in the progression of chronic gastritis to atrophic gastritis and intestinal metaplasia (*Fig. 4*) is becoming more apparent. Intestinal metaplasia is often associated with atrophic gastritis[10], and the links between both of these conditions and gastric cancer have been documented[21,22]. An animal model has shown that *Helicobacter* species can induce atrophic gastritis in mice[73]. Human studies have shown decreasing numbers infected with *H. pylori* as the mucosa changes from superficial gastritis to atrophic gastritis[74,75], but this may be accounted for by the environment within the stomach becoming more hostile to *H pylori* as atrophy progresses[72]. A study showing a relatively high prevalence of *H. pylori* serum antibodies and a low prevalence of *H. pylori* on histological staining of gastric biopsies in subjects with atrophic body gastritis, suggesting previous *H. pylori* infection, adds weight to this theory[76]. More recent studies, both histological and epidemiological, have shown a clearer association between *H. pylori*, atrophic gastritis[77,78] and intestinal metaplasia[79–82]. On balance, current evidence would suggest that progression to atrophy occurs by several routes and may involve a number of components[19], *H. pylori* playing a part but genetic[18,83] and environmental[10] factors likely to have a significant role. It is worth noting that *H. pylori*-associated antral gastritis and pangastritis are likely to account for a considerably higher proportion of individuals with mucosal atrophy than those affected by autoimmune gastritis[19]. A random sample of a rural Finnish population with an average age of 46 years found 2 per cent to have atrophic gastritis related to autoimmune disease, while another 10 per cent had atrophy most probably originating from *H. pylori* infection[19,83].

Helicobacter pylori and gastric cancer

Evidence for a causal relationship between *H. pylori* and gastric cancer comes from three main sources. Many of the data may be described as circumstantial, as might be expected of a process which takes 30 years or more to complete.

Epidemiology

A number of populations from various parts of the world with a high incidence of gastric cancer are now known to have high rates of *H. pylori* infection[53,61,84–86]. One extensive study involving 17 populations from 13 countries with contrasting gastric cancer risks has shown a significant relationship between seropositivity to *H. pylori*, and both the incidence and mortality rates of gastric cancer[62]. In parallel with gastric cancer rates[1], infection with *H. pylori* is lower in industrialized nations and is continuing to fall[50]. Infection with *H. pylori* and cases of gastric cancer are commoner in lower socioeconomic groups[61]. In developing countries, infection with *H. pylori* occurs in childhood and is life long[59]. Risk factors for gastric cancer have been demonstrated by migrational studies to be acquired at an early age[5,6].

It is the falling incidence of intestinal-type gastric cancer which largely accounts for a decreased overall rate of gastric cancer in the West[1]. This subtype is common in endemic gastric cancer areas[1] and is more closely linked with *H. pylori* in cross-sectional studies (see below). It has also been noted that the incidence of tumour of the cardia is increasing despite the downward overall trend[87–90]; these tumours are less clearly related to *H. pylori* infection[91,92].

There are a number of arguments against a relationship between *H. pylori* and gastric cancer. The male to female ratio for gastric cancer is approximately 2:1 whereas the ratio is closer to unity in *H. pylori* infection. *H. pylori*-associated chronic superficial antral gastritis is present in almost all patients with duodenal ulcer and chronic atrophic antral gastritis is present in many, yet duodenal ulceration is associated with a lower incidence of gastric cancer[93]. Furthermore, there are areas in the world, including most of Africa, where infection with *H. pylori* is extremely common, yet the incidence of gastric cancer appears to be low[94]. However, one of the authors (G.A.M.) has recently documented a relatively high incidence of gastric cancer, particularly in young people, in a highland region of Kenya: 3·1 per 100 000 in the 25–34-year age group and 5·7 in the 35–44-year age group.

Cross-sectional studies

These studies most often involve examining histological specimens or measuring immunoglobulin (Ig) G levels in patients with gastric cancer to look for evidence of *H. pylori* infection. The incidence of infection is then compared with that in controls who do not have gastric cancer. Some studies suggest that *H. pylori* infection is associated with gastric cancer[79,81,91,95–102]; others have found the proposed link does not reach statistically significant levels overall[92,103–108] and a few have shown no connection[75,109–111].

Generally, the studies showing no clear association have smaller numbers of cases of gastric cancer, usually fewer than 50. In some of these series the control groups are not representative of the general population, perhaps having a higher than average incidence of infection[104,105], but this is not always the case[92,103,109]. *H. pylori* infection is less common in advanced cancer[98], and it is important that histological examination for the organism is done well away from the tumour where the gastric environment may be more favourable to the infection.

Where the overall results are equivocal, analysis of subgroups is helpful. Tumours of the cardia have been suggested to be of a different aetiology and excluding these has demonstrated a better correlation of *H pylori* infection with tumours elsewhere in the stomach[91,92,101]. Correlation may be further enhanced by considering intestinal-type and diffuse-type tumours separately[91,99,104,112,113]. These studies show that intestinal-type tumours have a stronger link with infection, but this is not always the case[95,100,102,103,109,114–117]. Cancer occurring in a younger age group has been shown to have a more definite association with *H. pylori* infection[97,103,106,107,116].

Most workers suggest that cross-sectional studies are likely to underestimate the association, as the mucosa of the stomach becomes less favourable to *H. pylori* as the atrophic gastritis–intestinal metaplasia–dysplasia–cancer sequence progresses[91,98,115]. Supporting this view, the incidence of *H. pylori* in controls is found to increase slowly with age, while in patients with cancer, who have higher overall infection rates, evidence of infection decreases with age[95,97,103]. Furthermore, *H. pylori* is strongly associated with precancerous lesions in high-risk populations[45,80,105] and early tumours[102,107,113].

All these reports, with their various interpretations, demonstrate the inherent weakness in cross-sectional studies of a disease process which may take 30 years or more from its initiation to the final outcome. Taken in isolation, these papers provide only weak evidence of an association between *H. pylori* infection with all types of gastric cancer. A more positive correlation with non-cardia cancers and perhaps with intestinal types may be present.

'Prospective' studies

Missing from the evidence so far is a convincing demonstration that *H. pylori* infection will predispose an individual to developing gastric cancer 10–30 years later. There are now four nested case–control studies reported which have investigated the relationship between *Helicobacter* infection and the subsequent development of gastric cancer using serum samples stored up to 30 years previously. The first to appear[118] found 29 cases of gastric cancer had developed among a population of 22 000 men in England and Wales for whom stored serum was available. Seropositivity for *H. pylori* was significantly higher in cases of gastric cancer than in well matched controls. Two similar studies have been reported from the USA, one using stored serum from a medical care programme in California[93] and the other using serum from a cohort of Japanese American men living in Hawaii[119]. A fourth study has recently been reported from Finland[20], where the presence of IgA rather than IgG antibodies to *H. pylori* was associated with an increased risk of developing gastric cancer. Combining the results from the first three investigations suggests that infected individuals have almost a fourfold risk of developing gastric cancer when compared with controls (odds ratio 3·8 (95 per cent confidence interval 2·3–6·2))[120]. However, considering a subgroup from these studies, for which the interval between the original serum collection and the development of gastric cancer was 15 years or more, suggests that the relative risk may be nearer ninefold.

Helicobacter pylori and gastric B-cell lymphoma

There is little doubt that *H. pylori* has a major role in the pathogenesis of this rare tumour. The stomach does not normally contain organized lymphoid tissue but mucosa-associated lymphoid tissue (MALT), resembling intestinal Peyer's patches, appears in response to *H. pylori* infection[121,122]. MALT may then give rise to primary low-grade B-cell gastric lymphomas[123]. Parsonnet and colleagues[124] demonstrated that patients with gastric lymphoma were significantly more likely than matched controls to have evidence of previous *H. pylori* infection. An *in vitro* study revealed that proliferation of cells from gastric B-cell MALT lymphomas is stimulated by specific strains of *H. pylori* through activation of T cells[125]. Lymphomas from other sites were unaffected by exposure to *H. pylori*. Recent clinical trials have shown low-grade gastric B-cell lymphomas to be responsive to antibiotic eradication therapy for *H. pylori*, with complete regression for over 1 year in the majority of cases[126,127].

Pathogenesis of gastric adenocarcinoma

A picture is now emerging of the possible place of *H. pylori* in the development of gastric cancer (*Fig. 5*). The majority of those infected will remain asymptomatic with chronic active gastritis. Some will develop peptic ulcers and a few individuals will develop B-cell lymphoma. A minority will progress to atrophic gastritis, intestinal metaplasia, dysplasia and cancer. What determines the course of the disease in an individual is largely unknown, but some clues are available. *H. pylori* strains are known to be extremely diverse and characteristics of some have been identified which may predispose to increased inflammation and peptic ulceration[128]. Recent work has suggested that strains producing a vacuolating cytotoxin are associated with the development of atrophic gastritis and gastric cancer[129–131]; early age of acquisition of the infection may also be a significant factor[19,86,134,135]. The association of peptic ulcer disease with blood group O and gastric cancer with blood group A is well known, and it is likely that genetically inherited responses to inflammation will determine the outcome of infection[136]. Host response is known to be important in other chronic infections[137] such as leprosy. Environmental co-factors, particularly nitrates, salt and vitamin C, may also affect the outcome of the disease. Several mechanisms whereby *H. pylori* may be involved in the development of gastric carcinoma have now been postulated.

First, chronic inflammation has long been associated with the onset of a number of malignancies where increased proliferation of cells increases the risk for spontaneous DNA replication error. *H. pylori* has been shown to increase cell proliferation in the gastric epithelium[138,139]. Lymphocytes within the infected gastric mucosa may induce expression of growth regulatory peptides in gastric epithelial cells through the release of cytokines[140,141]. Mucosa from around early and late gastric carcinoma, areas of hyperplasia, intestinal metaplasia and dysplasia were compared with non-carcinoma control samples in a recent study[142]; the expression of transforming growth factor alpha and epidermal growth factor was found to be increased when compared with controls.

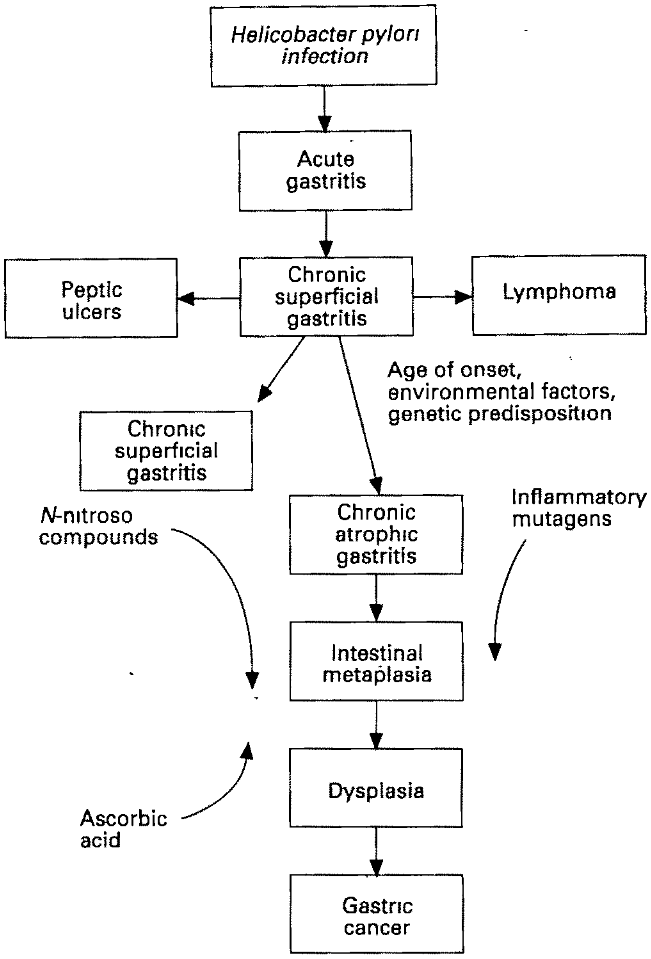
Helicobacter pylori infection
Acute gastritis
Peptic ulcers
Chronic superficial gastritis
Lymphoma
Age of onset, environmental factors, genetic predisposition
Chronic superficial gastritis
N-nitroso compounds
Chronic atrophic gastritis
Inflammatory mutagens
Intestinal metaplasia
Dysplasia
Ascorbic acid
Gastric cancer

Fig. 5 Model of pathogenesis of gastric cancer

Second, *H. pylori*-associated chronic gastritis is characterized by a heavy infiltration of inflammatory cells, including neutrophils. These cells migrate through to the surface of gastric epithelium where they ultimately degenerate[143], releasing radicals capable of damaging all four DNA bases of replicating cells[144]. Reactive oxygen species are increased in *H. pylori*-associated gastritis and eradication of the infection has been shown to reduce the activity of these free radicals[145].

The third contribution to the process is likely to be environmental factors[146]. *N*-nitroso compounds, for example, might act on the already stimulated epithelium to promote cancer. Dietary antioxidants, such as vitamin C, may reduce the amount of *N*-nitroso compounds within the stomach[29], but the presence of *H. pylori* has been noted to reduce ascorbic acid concentration in the stomach[147,148].

Future directions

The available evidence suggests that, while development of gastric cancer is a multifactorial process, *H. pylori* plays an important role, not least in the early stages of neoplastic development. The case is strong, by final proof must await the demonstration of prevention of gastric cancer by treatment of the infection. Reversal of metaplastic changes in the epithelium of the stomach by elimination of *H. pylori* has already been documented in a study in South America[149]. Successful eradication of the organism has been noted to reduce the gastric mucosal proliferative rate to normal[138]. Further opportunities for study exist in parts of Africa: why do some areas have a high incidence of cancer, particularly in young people, and other areas have a low incidence, despite an overall extremely high prevalence of *H. pylori* infection?

If the suggested mechanisms are correct, *H pylori* may be responsible for between 60 and 70 per cent of all gastric cancers[93,150]. The possibility then arises for prevention of the disease by the eradication of *H. pylori* from the infected stomach. A prospective trial is already under way, examining the effect of eradication of *H. pylori* and vitamin C supplementation on intestinal metaplasia[151], but it is likely to be some time before results are available.

Before launching a programme to eradicate *H. pylori* on a large scale, a careful analysis of the most efficient method of treatment is required, along with further evidence of the benefits to be gained. Eradication therapy for *H. pylori* has now been reduced to 1 week by using omeprazole in combination with metronidazole and either clarithromycin or amoxycillin, with a success rate of almost 90 per cent[152–155]. Antimicrobial therapy for all those affected is impractical, however, and would have unacceptable side-effects. Targeting populations at high risk may be helpful[156] but the best method of finding these individuals within low-risk populations has yet to be identified. Serology for *H. pylori* coupled with pepsinogen ratios to detect mucosal atrophy[157,158] might be one way forward.

Treatment in developing countries, where the largest potential benefit may be achieved, is complicated not only by economic constraints but also by widespread metronidazole resistance. Poor eradication rates have been noted in communities at high risk of gastric cancer[159], with metronidazole resistance an important cause of treatment failure[160]. Reinfection following treatment is common, probably from close family members[161]. High numbers of the organism in the gastric mucosa are associated with low eradication rates[162]. Attempts to develop a vaccine are under way[163] and currently offer the best hope of a significant reduction of gastric cancer in poorer communities. However, the injustice of health economics is likely to ensure that such a vaccine will benefit mainly affluent populations least at risk.

Acknowledgements

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Review

Neutropenic colitis: a continuing surgical challenge

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Background Neutropenic colitis is a clinicopathological syndrome characteristically seen as a complication of chemotherapy for haematological malignancy. This review explores the pathogenesis of the condition and appraises the options for management.

Methods A Medline search was carried out and all relevant papers were reviewed.

Results There are many case reports but few published series, so experience is mainly anecdotal. Both medical and surgical management have been successful; it is not possible to compare treatment groups formally.

Conclusion The greater use of aggressive multiagent chemotherapy regimens may increase the frequency with which the condition is encountered. Heightened awareness of neutropenic colitis may prompt diagnosis and a better understanding of the pathophysiology may help guide clinical management.

Neutropenic colitis is a clinicopathological condition characterized by a septic or inflammatory intra-abdominal process in patients with haematological malignancy or who are neutropenic for a variety of other reasons. The association of enteropathy together with haematological malignancy can be traced back to 1933 when Cooke[1] described the presence of submucosal haemorrhage and appendiceal perforation in children with leukaemia. Since then, the association of necrotizing lesions of the colon in patients with haematological malignancy has become more commonly recognized[2–4]. It is highly probable that the pathological process referred to in these early reports is that which is now termed neutropenic colitis. Rather than being a specific disease entity, neutropenic colitis probably represents a syndrome of pathological changes This may explain the abundance of other terms such as typhlitis[5], ileocaecal syndrome[6], necrotizing enteropathy[2] and necrotizing colitis[7]. Early case reports were based on autopsy findings but, as the clinical condition became clearer, it was more widely recognized on clinical grounds alone.

It is probable that neutropenic colitis is increasing in incidence. A major reason is the greater use of multiagent, aggressive chemotherapeutic regimens for the treatment of neoplastic disease and the consequent neutropenia that may occur following such treatment. The majority of cases occur in patients with acute leukaemia, haematological and other malignancies who undergo treatment with antineoplastic chemotherapy[2,7–9]. Rarely, it has been reported in patients with solid tumours of the colon, breast, lung, testis and pancreas who have received chemotherapy[10–13]. It has also occasionally been reported in neutropenia unrelated to chemotherapy but from other causes[14–17], and associated with aplastic anaemia[18]. Despite the condition being increasingly recognized and reported, the aetiology, pathogenesis and optimal clinical management of neutropenic colitis remain unclear. What is apparent is that the expansion of chemotherapeutic regimens in the management of haematological neoplasms and other solid cancers may result in a continuing increase in the frequency with which this condition is encountered.

Pathogenesis

Irrespective of the initiating aetiological factor, the pathological process appears to have a predisposition for the terminal ileum, appendix and caecum, hence its alternative nomenclature. Immunohistochemical studies of the gut in patients with leukaemia demonstrate infiltration of the mucosa by leukaemic and lymphoproliferative cells[19,20]. These deposits are more likely to result in ulceration following chemotherapy. By contrast, metastases from solid tumours are more likely to involve the serosal surface and this may explain the relative rarity of this condition in solid tumours treated with antineoplastic chemotherapy

Damage to the ileocaecal mucosa is probably the initial injury and is almost certainly multifactorial. The onset of clinical signs suggesting neutropenic colitis immediately following the administration of cytotoxic agents supports the contention that drug-induced mucosal injury plays a significant role in the initiation of the pathological process. The gastrointestinal mucosa represents a subset of highly proliferative cells. Cytotoxic chemotherapy inhibits cellular replication; mucosal proliferation may be insufficient to replace that which is lost by natural desquamation and so mucosal integrity may be lost. Other factors, including local bacterial or fungal infection with mucosal injury, necrosis of mural leukaemic infiltrates and mucosal ischaemia from sepsis-induced hypotension may all contribute to initiating mucosal injury[6,21]. Among the many cytotoxic agents thought to promote mucosal damage is cytosine arabinoside, which is used as part of combination regimens and is known to cause a spectrum of damage ranging from cellular atypia to frank ulceration[22].

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Neutrophils have been implicated in playing a crucial role in the development and full manifestation of several forms of injury to the upper gastrointestinal tract[23,24]. A definitive role for neutrophils in the development of colonic mucosal injury remains equivocal and, in the present context, somewhat intriguing given the presence of neutropenia. Indeed, experimental evidence suggests that inducing relative neutropenia in rats before the creation of colonic injury by the application of 4 per cent acetic acid failed to attenuate the severity of the macroscopic injury observed 24 h later[25]. Beull and Berin[26] studied three different models of experimental colitis in rats made neutropenic by the intraperitoneal administration of rabbit antirat neutrophil antiserum and found that neutrophils were neither actively involved in nor a major prerequisite for colonic mucosal injury. These experimental findings help to provide some scientific foundation for the clinical observation of colonic mucosal injury despite the presence of neutropenia.

It is not entirely clear why the caecal mucosa is predisposed to neutropenic colitis. Some[21,27,28] have suggested that this may be a consequence of the reduced blood flow to the colon compared with the rest of the gastrointestinal tract[29,30]. This may then be further exacerbated in the caecum where a degree of distension may increase intraluminal pressure and thereby compound the relative submucosal ischaemia. Once the primary mucosal damage has occurred, a variety of secondary events may follow, the most common of which is sepsis. Secondary sepsis arises as a result of defects within the intestinal mucosa and this itself may cause further tissue necrosis leading to bowel perforation and peritonitis. Secondary sepsis may also result in bacterial translocation and septicaemia. Blood cultures are often positive, the common pathogens isolated being *Clostridium septicum*[14,31–33], *C. difficile*[18,34], *Escherichia coli*[10,35], *Pseudomonas* spp.[10], *Klebsiella*[36,37] and *Enterobacter*[11]. Less frequently, *Candida* may be isolated[37,38] and in many cases more than one organism may be implicated.

Clinical presentation

Neutropenic colitis characteristically presents in adults and children with haematological malignancy who, by complication of chemotherapy for their malignancy, become neutropenic[6,39,40]. Neutropenia appears to be the prime underlying risk factor as the condition is also seen in other instances of neutropenia induced by chemotherapy for solid neoplasms[11,41–43], aplastic anaemia[18,36,44] and has also been seen in cyclic neutropenia[15,31], bone marrow transplantation[45], sulphasalazine usage for the treatment of rheumatoid arthritis[46] and in patients with acquired immunodeficiency syndrome[47]. The incidence varies between series. Moir and Bale[4] found that neutropenic colitis was a major cause of death in 19 of 50 consecutive autopsy studies in patients with leukaemia. Mower *et al.*[8] reported an incidence of 2·6 per cent in a series of 499 adults with acute leukaemia. By contrast, values of 33 and 46 per cent have been quoted by Shamberger *et al.*[48] and Steinberg *et al.*[9] respectively. Some of this variability may be accounted for by the difficulty in differentiating neutropenic colitis from other intestinal pathology, such as pseudomembranous or ischaemic colitis[7], particularly in patients managed non-operatively who have a successful outcome.

Symptoms and signs

Symptoms are non-specific and include nausea and vomiting, abdominal discomfort and distension, and diarrhoea which may be bloody. Nearly always, the episode will follow a course of antineoplastic chemotherapy and occur during a period of neutropenia, classically beginning 7–10 days after treatment. There is usually pyrexia, although this in itself is a non-specific sign as more than 90 per cent of neutropenic patients who are in hospital will be pyrexial at some stage[3]. Similarly, diarrhoea may result from the side-effects of vincristine or cytarabine therapy[22]. By an unknown mechanism, leukaemia *per se* may produce a clinical picture similar to that of an acute abdomen[3]. In neutropenic colitis, abdominal pain and pyrexia are associated with right iliac fossa tenderness in 60–80 per cent of patients and, in the later stages of the pathological process, there may be local peritonitis[7,49]. Later still, generalized peritonitis may ensue. There may be a mass palpable in the right iliac fossa or the lower abdomen and this usually represents a thickened, dilated, fluid-filled caecum. It may also represent an ileocaecal inflammatory mass or a localized collection around a perforated caecum or appendix. However, even in the presence of severe sepsis, physical findings may be minimal and, indeed, rapid progression to fulminant septicaemia may precede the development of these abdominal signs. This aggressive presentation of the disease is usually rapidly fatal.

Diagnosis

A high index of suspicion remains the key to diagnosis as a significant number of cases are diagnosed only after death[4]. The occurrence of abdominal symptoms in a neutropenic patient should alert the clinician, even in the presence of the most minimal physical signs. Further investigations are aimed at excluding other causes of an acute abdomen which may require a different management approach. A full blood count may reveal thrombocytopenia as well as neutropenia. Blood cultures are positive in more than half of all cases, with bowel organisms most frequently being isolated[28,31,44]. Although of theoretical benefit in the diagnosis of other acute colitides which may mimic neutropenic colitis[44], endoscopic examination of the bowel is usually avoided for fear of inducing further haemorrhage or perforation. Mechanical trauma from the procedure may also cause further mucosal damage, thereby increasing bacterial translocation and exacerbating septicaemia. Peritoneal lavage may be helpful in confirming the diagnosis as Gram staining of the recovered peritoneal fluid may reveal polymicrobial contamination[50,51].

Radiology

A plain radiograph of the abdomen may be useful if there are positive signs. Distal small bowel obstruction, thickening of the bowel wall, a right-sided soft tissue mass, or a gasless abdomen or right lower quadrant are all suggestive features[42,52]. Localized or diffuse 'thumbprinting', characteristic of mucosal oedema, may be noted and, in patients with enteric perforation, intraperitoneal free gas may be present. Pneumatosis intestinalis may also be observed in these cases[31,53]. Ultrasonographic findings consistent with a diagnosis of neutropenic colitis are of a rounded mass with dense central echoes and a wider hypoechoic periphery[54]. Ultrasonography may also demonstrate pseudopolypoid changes of the caecal mucosa and a pericolic fluid collection[42,55]; it has been suggested that it may be used to monitor the daily progression of the process[56]. Computed tomography (CT) findings are similar to those seen on ultrasonography but CT may be more accurate in determining caecal wall thickening[57–60]. Angiography performed in such circumstances demonstrates hypervascularity of the caecum, intense mucosal staining, arteriovenous shunting into the mesenteric veins and opacification of superficial mucosal ulcers[61]. Barium studies were performed in earlier series and in the presence of neutropenic colitis may demonstrate caecal distension, rigidity and mucosal oedema[19,52]. They are now avoided because of the theoretical risk of enteric perforation and because they provide little additional information over that available from ultrasonography or CT.

Management

Because many reports contain small numbers of patients it is difficult to be dogmatic about the most appropriate management. The optimal treatment of patients with neutropenic colitis, therefore, remains controversial. Advocates of a conservative approach cite the high operative morbidity and mortality rates[6,62]; a conservative policy can be successful[37,38]. The success of operative management and the difficulty in distinguishing neutropenic colitis from acute appendicitis have led others to advocate surgery strongly[12,63–65]. Wade *et al.*[66] succinctly summarize the situation thus: 'To categorically state that all cases need to be surgically treated or that all cases should be treated conservatively is an unacceptably simplistic approach. We think that each case should be treated individually'.

Neutropenic patients with abdominal pain present a particular challenge because of their increased susceptibility to infection and the rapidity with which

Table 1 Management and outcome of neutropenic colitis

Reference	Year	No. of patients	Medical management		Surgical management	
			n	Death	*n*	Death
Sherman and Woolley[6]	1973	11	8	8	3	1
Rasmussen and Freeman[69]	1975	2	—	—	2	0
Matolo *et al.*[74]	1976	4	—	—	4	4
Kies *et al*[72]	1979	2	—	—	2	0
Varki *et al.*[35]	1979	1	—	—	1	0
Lea *et al*[75]	1980	2	—	—	2	0
Lehman and Armitage[76]	1980	2	—	—	2	0
Pokorney *et al*[36]	1980	1	—	—	1	0
Dworkin *et al.*[77]	1981	1	1	0	—	—
Ikard[27]	1981	1	—	—	1	0
Abramson *et al.*[39]	1983	5	1	0	4	1
Gandy and Greenberg[38]	1983	2	2	0	—	—
Schaller and Schaller[64]	1983	4	—	—	4	1
Mulholland and Delaney[18]	1983	4	1	1	3	1
Shaked *et al*[62]	1983	2	1	0	1	1
Alt *et al.*[63]	1985	2	—	—	2	0
Kunkel and Rosenthal[49]	1986	3	—	—	3	2
Moir *et al.*[37]	1986	16	10	5	6	2
Mower *et al*[8]	1986	13	5	5	8	0
Shamberger *et al.*[48]	1986	25*	21	1	6	1
Starnes *et al.*[10]	1986	5	4	0	1	0
Villar *et al.*[65]	1987	19	15	14	4	1
Skibber *et al.*[78]	1987	16	3	3	13	1
O'Brien *et al.*[79]	1987	7	7	0	—	—
Baniel *et al*[80]	1988	3	1	0	2	1
Koea and Shaw[28]	1989	3	—	—	3	0
Merine *et al*[81]	1989	1	1	1	—	—
Cutrona *et al.*[47]	1991	2	2	0	—	—
Chakravarty *et al*[46]	1992	1	—	—	1	1
Wade *et al.*[66]	1992	22	16	11	6	3
Vohra *et al.*[12]	1992	3	—	—	3	1
Or *et al.*[45]	1992	1	1	1	—	—
Weinberger *et al.*[44]	1993	2	—	—	2	0
Chubachi *et al*[82]	1993	1	1	0	—	—
Bajwa *et al.*[83]	1993	1	1	1	—	—
Dudiak *et al.*[84]	1993	1	1	0	—	—
Coleman *et al.*[85]	1993	1	—	—	1	0
Anderson[86]	1993	1	—	—	1	0
Suarez *et al.*[87]	1995	1	1	0	—	—
Stein *et al.*[13]	1995	1	1	1	—	—
Total		195	105	52 (50)	92	22 (24)

Values in parentheses are percentages. *Twenty-seven episodes in 25 patients such sepsis can become overwhelming. Indeed, infection remains the leading cause of death in patients with haematological malignancy[67] and frequently the causative organisms are Gram-negative bacilli of autogenous gastrointestinal origin[68]. The situation is further compounded for the attending surgeon because many of the accepted criteria for surgical intervention, e.g. fever and leucocytosis, may not necessarily be present or, if present, may be of limited clinical value. The knowledge that surgery is followed by greater morbidity and mortality rates in these patients because of co-existing medical problems further complicates decision making[42,69].

Few would argue that initial management should be by fluid and electrolyte replacement and resuscitation, together with administration of broad-spectrum antibiotics, appropriate blood products and inotropic support if required. Frequently this initial management is undertaken in the intensive care setting. Gastrointestinal decompression by a nasogastric tube and restriction of oral intake are also probably beneficial. Parenteral nutritional support may be required Once this initial period of resuscitation has been completed the real dilemma begins. No one would argue that free intraperitoneal perforation, generalized peritonitis and continued bleeding despite correction of any coagulopathy are indications for surgery. The underlying disease process may also affect the management decision in that one would probably be more aggressive in recommending surgery for a patient with leukaemia who is receiving induction chemotherapy than for a patient with leukaemia who has end-stage disease[66]. In the absence of hard indications for surgery, an initial attempt at medical treatment is reasonable. This, however, requires repeated clinical assessment by the same surgeon and frequent radiographic evaluation to chart the disease process. Should the clinical condition deteriorate (increasing inotropic requirement, increasing fluid sequestration or the appearance of any of the above indications for surgery), an operation should be performed. If there is no deterioration, medical treatment should continue until the neutropenia resolves. Bone marrow recovery may be accelerated by the administration of recombinant granulocyte colony-stimulating factor, which may have a role in the treatment of this condition[70]. Following successful medical management of an episode of neutropenic colitis, especially if this has occurred at induction therapy, the condition may recur during future cycles of chemotherapy; such episodes frequently result in surgical intervention[37,71].

Once a decision to operate has been made, the question of which procedure is a source of debate. Most authors agree that right hemicolectomy is the operation of choice[8,28,63,72]. Less extensive surgical interventions, such as appendicectomy or caecostomy, may be inadequate in the management of neutropenic colitis as the extent of mucosal necrosis may often be greater than that which is obvious by inspection of the serosa[22,49]. At operation, the surgeon must also decide whether to perform an end-to-end anastomosis or to exteriorize the bowel. Primary anastomoses have been unsuccessful in some cases[40,65] but in others have healed satisfactorily[4,63,64,66,73]. Clearly in such circumstances, basic surgical principles apply. If extensive sepsis or significant peritoneal soiling is present, primary anastomosis is probably inappropriate. In this situation an end ileostomy and mucous fistula is advisable.

Outcome and prognosis

The reported results are presented in *Table 1*. There are approximately equal numbers in the medical and surgical groups. Those treated surgically appear to have a better outcome, but caution must be exercised as the two groups are almost certainly not comparable. It may be that medically treated patients were generally more debilitated to begin with and may have been deemed unfit for surgery. Although earlier surgical intervention may potentially be advantageous, it is impossible to substantiate this from the published literature despite an earlier review of 21 cases which concluded that surgery was more effective than medical treatment alone[88]

Conclusion

Neutropenic colitis remains a major clinical challenge. With the greater use of aggressive multiagent antineoplastic chemotherapy, it is likely to be encountered with increasing frequency. What is clear from a review of the literature over the past three decades is that there is no obvious superiority of medical over surgical management. Recognizing the condition and confirming the diagnosis by clinical and radiological investigation remains the initial challenge. Once the diagnosis has been made, a knowledge of the natural history of the condition should help the clinician to manage the patient on an individual basis according to the prevailing symptoms and signs.

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Review

Recurrent carotid stenosis after carotid endarterectomy

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Background This review examines the history, incidence, aetiology and pathology of recurrent carotid stenosis, and assesses the methods and results of managing patients with this condition.

Methods Over 200 references were retrieved from Medline from 1966 to 1996. Data were collected which reported the incidence, timing, method of diagnosis, follow-up, percentage of patients with symptoms and the indications for revisional surgery. The stroke rate and operative mortality rate following revisional carotid surgery were also recorded.

Results The overall incidence of symptomatic recurrent stenosis ranged from 0 to 8·2 per cent, with a symptomless recurrence rate between 1·3 and 37 per cent. Forty-three (78 per cent) of 55 studies indicated that revisional surgery was performed on patients with symptoms; only 21 (38 per cent) of 55 studies indicated that operations were carried out on asymptomatic patients. The stroke rate and mortality rate after 511 revisional procedures were 3·9 and 1·0 per cent respectively.

Conclusion Symptomatic recurrent stenosis is rare but some patients may benefit from revisional surgery. Surgery for symptomless carotid restenosis should be considered only if a multicentre trial can demonstrate clear benefit in terms of patient survival or stroke reduction.

Carotid endarterectomy is now accepted as an effective therapy for the management of transient ischaemic attacks and for prevention of future strokes in patients with severe stenosis of the internal carotid artery[1–5]. The indications for operating on the symptomless patient with a high-grade stenosis remain controversial and trials are still in progress to clarify this issue[6–8]. The management of recurrent carotid stenosis after carotid endarterectomy remains even more of a dilemma. This is partially the result of differing methods of assessment, disease classification and definitions of recurrent stenosis, but one is also hampered by the fact that only small numbers of patients require surgery for recurrent stenosis at individual centres. Carotid endarterectomy is already the commonest peripheral vascular procedure performed in the USA[9]. In the wake of the reports of the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[1] and the European Carotid Surgery Trial (ECST)[2] advocating carotid endarterectomy for symptomatic high-grade stenosis, the number of patients worldwide developing recurrent stenosis is set to increase.

History

Recurrent stenosis of the carotid artery was first documented 14 years after the original case report of the operation by Eastcott *et al.*[10] in 1954. Edwards *et al.*[11], using angiography, in 1968 found three arteries had restenosed of 43 that had had a carotid endarterectomy. Stoney and String[12] reported the first large series of patients operated on for recurrent carotid stenosis. They followed 1654 carotid endarterectomies in patients for between 5 months and 13 years. Revisional surgery was carried out for recurrent symptoms in 27 patients. Two symptomless patients also had further procedures when a tight stenosis was found following the appearance of a new bruit. Intimal fibrosis at the site of the endarterectomy was usually responsible for restenosis within 2 years of operation and recurrent atheroma after 2 years.

Definition and measurement

Recurrent stenosis in its broadest sense means any arterial narrowing developing at or near the site of an operative or interventional procedure to treat an atheromatous stenosis. Residual disease, a neighbouring stenosis and an intraoperative flap with mural thrombus have all been included under the general term of recurrent restenosis. Purists[13] advocate that some form of intraoperative or early postoperative imaging is essential as a baseline[14], so that any subsequent changes can be identified and any residual abnormalities can be excluded. As this policy has rarely been adopted and the diagnosis of restenosis relies on a variety of imaging techniques which only really outline the arterial lumen, it is hardly surprising that there are considerable differences in the published incidence of recurrent stenosis[15] (*Table 1*).

The value of any definition is to a considerable extent determined by the methodology on which it is based. There is no accepted standard for quantification of the primary carotid stenosis and this has to be agreed before consideration can be given to the measurement of recurrent carotid stenosis. The NASCET[1,68] criterion for determining carotid stenosis was based on comparing the diameter of the residual lumen at the point of maximum stenosis with the diameter of the internal carotid artery well beyond the bulb. A jeweller's eyepiece with a submillimetre scale was used to measure biplanar selective-catheter carotid angiograms. This method was also used in the Asymptomatic Carotid Atherosclerosis Study (ACAS) and has been recommended by the standards subcommittee of the Society of Vascular Surgery[69]. The

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Table 1 Incidence of recurrent stenosis in published series

Reference	Year	No. of arteries	Mean follow-up (years)	Restenosis (%)	Symptomatic (%)	Revision in asymptomatic patients*	Diagnostic method
Stoney and String[12]	1976	1654	9	1·7	1·6	Yes	Symptoms/bruit
Hertzer *et al.*[16]	1979	1250	3·8	1·3	1·0	Yes	Symptoms/bruit
Kremen *et al.*[17]	1979	173	6	9·8	1·7	Yes	OPG
Turnipseed *et al*[18]	1980	70	1·5	9	3	—	Duplex
Cantelmo *et al*[19]	1981	199	1·7	12·1	4·5	HGS, CICO	OPG/CPA
Callow[20]	1982	886	1	—	1·7	—	Symptoms
Zierler *et al.*[21]	1982	89	1·3	19	5	Clinical	Duplex >50%
Norrving *et al.*[22]	1982	—	6	36	—	—	Duplex
Baker *et al*[23]	1983	133	5	9·7	1·5	>75%	OPG, CPA, POD
Salvian *et al.*[24]	1983	105	2·3	11·4	4·8	No	OPG
Shanik *et al.*[25]	1983	80	1·8	13	1	No	Duplex >50%
Thomas *et al*[26]	1984	257	1·7	8·9	1·2	HGS	Duplex >50%
Colgan *et al*[27]	1984	80	1·8	13	1	No	Duplex >50%
Pierce *et al*[28]	1984	75	2·4	5	3	—	—
Das *et al*[29]	1985	1726	4	3·8	8·1	—	DSA
Hamann *et al*[30]	1985	798	6·5	3·4	—	—	Duplex/DSA
O'Donnell *et al.*[31]	1985	276	3·2	12·3	1·4	HGS	B-mode
Nicholls *et al*[32]	1985	145	1·5	17–22	1·4	No	Duplex >50%
Glover *et al.*[33]	1985	131	4	11·4	—	—	Duplex
Keagy *et al.*[34]	1985	122	—	22	—	—	Duplex/POD
Piepgras *et al.*[35]	1987	1935	6	2·9	2·7	HGS	OPG/Angio
Zbornikova *et al.*[36]	1986	113	—	23·9	4·4	—	Duplex >50%
Courbier *et al*[37]	1986	100	1·6	9	—	—	DSA >50%
Sundt *et al.*[38]	1986	99	2	5	—	—	DSA
Barnes *et al*[39]	1986	47	—	6	0	—	Doppler >50%
Hunter *et al.*[40]	1987	370	2·3	8·9	6·8	>80%	Symptoms/bruit
Ouriel and Green[41]	1987	102	1·4	13·7	0	—	Duplex >50%
Sanders *et al.*[42]	1987	94	1	7	—	—	Duplex >50%
Katz *et al*[43]	1987	89	1·6	11	3	>75% Angio	Duplex >50%
Sanders *et al.*[42]	1987	84	1	7	—	—	DSA >50%
Curley *et al.*[44]	1987	72	1·8	14	3	HGS	Duplex >50%
Raj *et al.*[45]	1988	680	4·5	—	1·3	No	DSA
Civil *et al*[15]	1988	270	1·8	3–32	1·5	>70%	Duplex
Bandyk *et al.*[46]	1988	250	2	12	0	>75% CICO	Duplex >50%
Eikelboom *et al.*[47]	1988	129	>1	11	0	No	Duplex/DSA
Mattos *et al.*[48]	1988	117	1·3	14·5	5·1	>80%	Duplex >50%
Bernstein *et al*[49]	1990	484	3·5	8·5	—	>90% TCD	Duplex >50%
Healy *et al.*[50]	1989	301	4	19–26	3·7	No	Duplex >50%
Clagett *et al*[51]	1989	152	1·8	5·9	0·7	—	Duplex >25%
Sawchuk *et al.*[52]	1989	80	2·7	5	—	—	Duplex >50%
Sterpetti *et al*[53]	1989	73	—	37	8	—	Duplex >50%
Rosenthal *et al*[54]	1990	717	3·2	3·3	0·5	No	Duplex >50%
Atnip *et al*[55]	1990	184	3	6	1·6	>80%	Duplex >50%
Reilly *et al*[56]	1990	131	1·2	18·1	—	—	Duplex >50%
Cook *et al*[57]	1990	78	2·6	18	3	No	Duplex >50%
Nitzberg *et al.*[58]	1991	1043	3·9	—	1·8	>75%	Duplex >50%
Mattos *et al.*[59]	1992	544	3·7	12·7	2·8	—	Duplex >50%
Mattos *et al.*[60]	1993	409	3·5	10·8	2·7	>50%	Duplex >50%
Donaldson *et al*[61]	1993	232	1·4	18·5	1·7	>80% CICO	Duplex >50%
Powell *et al.*[62]	1993	107	1	16·8	2·8	No	Duplex >50%
AbuRahma *et al.*[63]	1994	973	2·6	—	3·4	>80%	Reoperation
Baker *et al*[64]	1994	316	1·8	4·7	0	—	Duplex >75%†
Myers *et al*[65]	1994	163	4·9	9·8	2·4	—	Duplex >25%
Katz *et al.*[66]	1994	100	3	2	—	—	Duplex >50%
Lattimer *et al*[67]	1996	482	6·5	17·0‡	2·3	No	Duplex >50%

*Indications for revisional surgery are given where possible, †area reduction; ‡2-year follow-up OPG, oculopneumoplethysmography; HGS, high-grade stenosis; CICO, contralateral internal carotid occlusion; CPA, carotid phonoangiology; POD, periorbital Doppler ultrasonographic assessment; DSA, digital subtraction angiography; Angio, angiography; TCD, transcranial Doppler assessment

ECST[2] criterion of carotid stenosis was based on the maximum percentage reduction in diameter of the relevant carotid artery. In this technique the normal arterial diameter is based on an assumption, and the interpatient and intrapatient variability in the position of the carotid bulb further complicates this measurement. Many other studies have now attempted to clarify the best method of measurement[70–72], but all techniques involve measuring stenosis diameter against various fixed reference points.

The introduction of carotid angioplasty[73,74] for dilating carotid stenosis could complicate any definition of carotid restenosis by introducing the many definitions that are currently used to measure restenosis following coronary artery angioplasty[75].

Brown and Johnston[76] on 119 biplanar angiograms have compared the minimal residual diameter with three other commonly used methods of quantifying stenosis: the calculated percentage area reduction, the percentage diameter reduction, and a qualitative estimation made by several radiologists. They concluded that measurement of the minimal residual internal diameter alone (corrected for angiographic magnification) most accurately reflected the severity of the disease. This method, which dispenses with any reference points and is more reproducible, could also be used for quantifying recurrent carotid stenosis.

The duplex ultrasonographic measurement of stenosis based on Strandness' criteria[77,78] in primary carotid disease is also currently applied in most studies defining recurrent stenosis in the follow-up of patients after carotid endarterectomy. A systolic peak velocity greater than 1·25 m/s (greater than 4 kHz) with marked spectral broadening throughout systole defines a stenosis of greater than 50 per cent diameter reduction, or 75 per cent area reduction. These duplex criteria are, of course, based on comparisons with angiography, which is usually assessed by the techniques already described rather than the true 'gold standard' which involves a luminal cast of the excised stenosis.

Incidence

The incidence of recurrent carotid stenosis is also a reflection of the methods used for its detection[20]. The introduction of more reliable non-invasive serial assessment by duplex scanning[21] has increased the proportion of patients with symptomless recurrent stenosis; such patients were previously surmised from carotid auscultation or oculopneumoplethysmography[17]. Repeat intra-arterial angiography is considered to be unethical because of the risk of stroke[79] and there are few studies of repeat intravenous digital subtraction angiography. Serial follow-up and life-table analysis has improved estimation of the true incidence of recurrent stenosis by taking into account the phenomenon of regression[50] and excluding residual defects visualized at completion of the endarterectomy[42]. Civil *et al.*[15] reported that the recurrence rate, which varied from 3 to 32 per cent, may be substantially influenced by the way the data are manipulated and grouped. In particular, the cohort of patients selected for analysis and the crude *versus* cumulative approach to the calculations allow for wide differences in incidence.

The incidence of recurrent stenosis reported in 55 publications has been examined and, as far as possible, included carotid occlusion and stroke within symptomless and symptomatic patients respectively (*Table 1*). The collective incidence of symptomless restenosis, defined in most series as a more than 50 per cent reduction in diameter on duplex scanning, ranges from 1 to 37 per cent. The proportion of patients with symptoms presumed to be due to stenosis ranges from 0 to 8 per cent. The criteria given by individual reports for revisional carotid surgery on patients with symptomless stenoses are also indicated and vary considerably from hospital to hospital.

Carotid angioplasty

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) has indicated that angioplasty may be a useful alternative to surgery for treating carotid stenosis[80]. Initial experience with balloon angioplasty for head and neck vessels was reported in the early 1980s[73,74,81]. Recent reports have demonstrated the safety, efficacy and long-term success of angioplasty, with a risk of stroke comparable to that for carotid endarterectomy[82], although this requires verification by other series.

Reported incidences of restenosis following this procedure are few as yet. Kachel[83] successfully dilated 57 carotid stenoses and after a mean follow-up of 65 months could not demonstrate any restenosis. Higashida *et al.*[84] carried out balloon angioplasty on 100 carotid stenoses with an overall restenosis rate of 5·5 per cent between 3 months and 7 years. Markus *et al.*[85] assessed carotid restenosis by using published duplex criteria 1 month after angioplasty in ten patients. Two patients were found to have stenoses greater than 50 per cent. This is the correct form of assessment and will probably show a higher restenosis rate than the early, and probably over-optimistic, reports, judged by the results of angioplasty at other sites.

Aetiology

Demographic factors

Most reports on follow-up after carotid endarterectomy have examined the influence that smoking, hyperlipidaemia, sex, age, hypertension and diabetes have on the development of restenosis. None has clearly demonstrated that any of the recognized risk factors for atherosclerosis contribute to the process of restenosis. Continued smoking probably has the greatest predictive value[46,51,53,62,86], but other reports have failed to confirm this relationship[41,55]. Furthermore, the failure to obtain an accurate smoking history from patients should be considered[87]. A relationship with female sex[26,31,32,41,50,86] is not consistent[55,62]. Hyperlipidaemia may contribute to restenosis[31,88-90] and lipid lowering trials have been proposed[91], but hyperlipidaemia is not always demonstrable[62,86]. Young age[86], diabetes[55], the severity of the original stenosis[26], the presence of symptoms at the time of the original operation[55], bilateral disease[19] and hypertension[89] have all been incriminated by individual reports, but have not been confirmed by others.

Defects detected at intraoperative assessment

Completion angiography[92,93], intraoperative duplex scanning[94,95] and angioscopy[96,97], used individually or in combination, are all methods which have been used to assess the technical success of carotid endarterectomy. The residual lesions that have been identified include atheroma, myointimal flaps, intraluminal thrombi, kinks, proximal 'shelves' of atheroma, vein patch irregularities and forceps marks. The incidence of unsuspected technical errors demonstrated by these techniques has varied from 5 per cent[98] through 22 per cent[95] to 65 per cent[37]. The authors of these reports have been divided as to whether abnormalities identified, if left uncorrected, contribute to restenosis.

Sawchuk *et al.*[52] reported a series of 80 carotid endarterectomies assessed by duplex scanning. Nineteen had 1–3-mm intimal flaps detected at operation, 16 of which resolved completely before the first postoperative ultrasonographic study. No statistically significant relationship could be shown between the presence of minor residual defects and the development of recurrent stenosis. Burnand and Lattimer[14], in a series of 35 consecutive carotid endarterectomies, attempted to correlate restenosis with peak intraoperative velocity measurement and estimations of stenosis on completion angiography (measured three ways). Neither investigation was able to forecast the development of restenosis with any predictability, although other centres[99] have demonstrated an increase in flow rate following carotid endarterectomy which may be predictive.

Baker *et al.*[64] in a similar series of 316 carotid endarterectomies found that 19·6 per cent of patients had residual abnormalities demonstrated on duplex scanning; 85 per cent were not re-explored because the defect was minor. A greater than 75 per cent area stenosis was found at follow-up (mean 21·6 months) in 17 per cent of the carotid arteries that had residual defects but in only 4·3 per cent of the endarterectomized carotid arteries that were judged satisfactory. It was concluded that even small defects appear to be associated with an increased incidence of late restenosis and that surgical technique is the most significant factor in preventing restenosis. Reilly *et al.*[56], in a similar study using intraoperative and postoperative duplex surveillance, correlated intraoperative defect size with the risk of recurrent stenosis ($P = 0{\cdot}0175$). The magnitude of this effect was small for the smaller defects. Courbier *et al.*[37] and Donaldson *et al.*[61] used completion angiography routinely, and demonstrated a reduction in both restenosis and reoperation when remedial action was undertaken at the time of the original surgery. Zierler *et al.*[21] also used operative angiography routinely and found that technical errors or residual stenoses were not major factors contributing to carotid restenosis.

Bandyk *et al.*[46] addressed the influence of turbulence on the development of restenosis. Some 4 per cent of patients (250 endarterectomy sites) had angiographic and Doppler flow abnormalities which, when explored, identified the presence of various defects. In arteries with residual flow disturbances identified at operation which were not corrected, the incidence of occlusion and recurrent stenosis rose from 9 to 21 per cent at 2 years.

Internal carotid artery size

In a series of 293 patients the mean internal carotid artery diameter measured with calipers at the time of surgery was 4·6 mm in men and 4·3 mm in women[51]. The significantly smaller size of the female carotid might explain the increased incidence of restenosis observed in women in a number of series[32,50,86]. This has led some surgeons to adopt a technique of obligatory patch closure in smaller vessels[51]

Ouriel and Green[41] in a series of 152 patients estimated the size of the internal carotid artery from preoperative angiograms by measuring the diameter of the contrast column beyond the area of disease. The patients were then followed for a mean of 17 months using duplex scanning. Small internal carotid arteries (less than 4 mm) had an increased risk of recurrent stenosis (37 *versus* 12 per cent) ($P < 0{\cdot}05$). In another study in which the internal carotid diameter was measured at the time of surgery using calipers, a 5-year cumulative restenosis rate of 5·3 per cent was noted after vein patch angioplasty of internal carotid arteries less than 5 mm in diameter; this compared with 14·3 per cent when arteries over 5 mm were patched[65].

Patch or direct closure

Ever since the first reports of successful carotid endarterectomy in the early 1950s[100–102] there has been considerable controversy regarding the optimum technique for closing the arteriotomy. The main theoretical advantage of patch closure is that it increases lumen size. The use of autologous vein as a patch material may provide an unwelcome additional source of proliferating smooth muscle cells but it may also provide the endarterectomized vessel with an additional source of endothelial cells[65].

Carson *et al.*[103] in 1981 ‘endarterectomized’ 40 healthy carotid arteries in an animal model. Half of the arteriotomies were closed with a jugular vein patch and the other half were closed directly with a continuous 6/0 polypropylene suture. After 6 months no evidence of fibrous intimal hyperplasia was found in any of these arteries when examined microscopically. The experiment was then repeated with polytetrafluoroethylene (PTFE) interposition grafts and patches. All the arteries either occluded or became stenotic. Fibrous intimal hyperplasia was found to be the cause.

The effectiveness of saphenous vein patch angioplasty in minimizing recurrent stenosis has been demonstrated by several authors[41,43,44,104–106]. Eikelboom *et al.*[47], in a randomized prospective study, compared patch angioplasty with primary closure and found that a vein patch prevented early recurrent stenosis caused by myointimal hyperplasia, as well as reducing recurrent atherosclerosis.

In contrast, many studies have demonstrated excellent results with primary closure[54,107]. Two randomized prospective studies have assessed both the short-term (mean 22 months) and long-term (5 years) effects of patch *versus* primary closure on restenosis[51,65]. The incidence of restenosis in the patched group was 12·9 per cent (early) and 14·3 per cent (late), and the respective values in the primary closure group were 1·7 and 7·8 per cent. The use of a vein patch was not shown to have any short- or long-term advantage when compared with primary closure.

Several reports have championed the use of PTFE patch angioplasty for carotid endarterectomy closure[54,106,108–111]. In a prospective randomized trial Katz *et al.*[66] compared the incidence of recurrent stenosis in a total of 100 carotid endarterectomies closed either primarily or with a PTFE patch. Only one patient had developed a restenosis of more than 50 per cent on serial duplex scanning by 36 months.

There is no consensus on the choice of vein or prosthetic material for the patch. A neck vein or the lower end of the saphenous vein has been reported to have a high risk of rupture[112], but it seems a pity to destroy the whole of the long saphenous vein for a few centimetres of its upper end. PTFE, therefore, has attractions, but its poor handling qualities, high incidence of suture line haemorrhage and potential thrombogenicity ensure that it does not have universal appeal. Dacron (Du Pont, Wilmington, Delaware, USA) has similar drawbacks. Even when the patch material has been selected, the width of the patch remains to be decided, patches may be cut wide (more than 5 mm) or narrow (3 mm) but a middle road seems appropriate. The above contradictory results have led many to use a patch only in selected patients, patches in general being applied when the vessel is less than 3·5 mm in diameter and shunt insertion is difficult or impossible.

Histopathology

The morphological appearance of the recurrent stenosis depends on the time interval following endarterectomy. Immediate lesions include residual disease and intraoperative flaps, early lesions (less than 2 years) are usually a result of myointimal hyperplasia and late lesions (greater than 2 years) usually consist of recurrent atheroma if the definition 'any stenosis following endarterectomy' is used. The presence of thrombus adds bulk to the restenotic lesion and may be an important part of the restenotic process[113].

Stoney and String[12] in 1976 reviewed 31 carotid endarterectomies with restenosis, and classified them according to the histological characteristics of the excised arterial wall and the site of the narrowing. All 11 patients with intimal fibrosis presented within 2 years of endarterectomy and in ten the stenosis developed in the endarterectomy bed. In contrast, 20 patients developed recurrent atheroma; all presented after 2 years and the plaques were more widely distributed along the artery. In one patient the recurrent carotid narrowing was caused by an external fibrotic stricture. Imparato *et al.*[114] and Callow[20] have suggested that the pathogenesis of recurrent carotid stenosis involves a dynamic process of early myointimal hyperplasia and late atherosclerotic degeneration, which explains the differing histological appearances.

Schwarcz *et al.*[115] studied 20 pathological specimens of carotid restenosis with light microscopy and immunoperoxidase staining to examine the endothelial and smooth muscle cells. Early stenoses had a greater cellular component with small nests of lymphocytes and polymorphs surrounded by dense accumulations of collagen and acid mucopolysaccharide. Needle-shaped cholesterol clefts, foam cells and extracellular fat became more apparent in the later lesions. Endothelial cells were found lining the luminal surface of both the early (38 per cent) and late (75 per cent) stenoses. Immunoreactivity for desmin and actin was found only in the early restenotic lesions (56 per cent). Capillary ingrowth (neovascularization) was evident in both the early (44 per cent) and late (75 per cent) specimens.

Hertzer *et al.*[16] used transmission electron microscopy to examine the myointimal cells. The abundance of rough endoplasmic reticulum was similar to that of fibroblasts and the linear microfilaments at the periphery of the cell were typical of smooth muscle cells. These cells are probably dedifferentiated smooth muscle cells[116]. It was concluded that myointimal fibroplasia was a direct collagenous extension of the media.

Pathogenesis

Response to injury

Restenosis is often considered a reparative response to arterial injury[20,117] Surgical manipulation, clamp injury, shunt trauma, radiological angioplasty and the placement of distal tacking sutures[24] all produce various degrees of injury. These all cause generation of tissue factor, activation of platelets and proteases, release of cytokines and growth factors, and mobilization of inflammatory cells. The extent to which this process is part of normal healing rather than an exaggerated response remains to be determined.

In 1981, Aukland and Hurlow[118] reported a recurrent stenosis in the common carotid artery at the site of an occlusive clamp which developed 19 months after an endarterectomy. A number of similar cases have subsequently been reported[40,119], one of which may have led to a stroke[54]. There is some experimental evidence that atherosclerotic stenosis can be induced in hyperlipidaemic animals in the areas where vascular clamps are placed[120]. When restenosis developed in the porcine coronary artery model its extent was proportional to the severity and depth of the vessel injury[121–123]. When arterial stents were deployed, the vessel injury score showed a highly significant linear regression with neointimal thickness[124]. ^{111}In-radiolabelled platelet deposition also equated with the severity and depth of the arterial injury in an angioplasty model[125]. A similar relationship between neointimal thickness and depth of arterial injury has been inferred in humans[126 127].

Thrombosis

Evidence is accumulating that thrombosis can occur at any time after endarterectomy. In 1967 Blaisdell *et al.*[92] reported that a quarter of their patients had unsuspected intramural defects suspicious of thrombosis on completion angiograms. Distal spasm may be one cause of this postendarterectomy thrombosis[128]. Furthermore, resorption of thrombus may explain the observation that some early lesions may undergo regression[21 23 32]. Acute occlusive and non-occlusive carotid thrombosis was found at reoperation in eight patients who presented with neurological deficits within the first 18 h after surgery[129]. Thrombus was thought to be the major component of the recurrent stenosis in eight of 57 reoperations[35]. In our retrospective series of 12 patients operated on for carotid restenosis, the presence of macroscopic thrombus was reported in three specimens (*Table 2*). Although vein patches have been advocated to prevent luminal narrowing and reduce thrombus formation[47 104,106 130], layering thrombus has been demonstrated in the dilated part of saphenous vein patches by duplex scanning[51,65] and by ^{111}In-radiolabelled platelet studies[131].

One hundred and nine internal carotid endarterectomies were followed with duplex scans and intravenous digital subtraction angiography to assess whether residual lesions encouraged the development of early recurrent stenosis[42]. Approximately half of the arteries with a significant narrowing at 1 year already demonstrated narrowing at 1 week after operation, although the composition of the stenosis was imprecise. A detailed histopathological study of 32 patients, which compared the composition of primary plaques and recurrent carotid disease, found that surface and intraplaque thrombus was present in 29 of the recurrent lesions ($P < 0{\cdot}001$). This study concluded that thrombosis was a continuous and intrinsic component of the recurrent disease rather than a secondary complicating feature[113]. Other investigators have not been able to confirm that thrombosis is a major factor in the development of recurrent stenosis[115].

The contribution of thrombosis to the process of restenosis has been examined in humans and in animal models by Schwartz *et al.*[117] and others[132,133]. Early events were studied in a dog model of carotid endarterectomy[134]. Immediately after blood flow was re-established a fibrin platelet carpet was seen to form over the endarterectomized segment. Mural thrombus caused by

Table 2 Original and recurrent presentation, timing, pathology encountered at revisional surgery, and method of repair and duplex follow-up of 12 patients with carotid restenosis

Patient no.	Sex	Age (years)	Side	First symptom	Second symptom	Time to reoperation	Date of reoperaion	Pathology	Operation	Velocity (m/s)	Date
1	F	56	L	AF	AF	3 years	5/86	Ath	End	—	—
2	F	59	L	AF	AF	10 months	3/87	MIH/Throm	VP	0·38	(1/95)
3	F	59	L	AF	AF	12 years	5/87	Calc	End	3·27	(4/95)
4	M	37	R	CVA	AF	22 months	8/87	Ath/Throm	End, VP	0·54	(3/91)
5	M	49	R	AF	AF	11 years	6/89	Ath/Ulc	End	0·37	(11/94)
6	M	51	R	AF	AF	12 years	11/89	Ath	End, VP	—	—
7	F	52	R	TIA	AF	4 years	1/90	Ath/Throm	End, VP	1·30	(2/95)
8	M	62	L	AF	TIA	9 years	1/92	Ath	VP	0·94	(7/94)
9	F	60	R	AF	AF	6 years	8/92	Ath	VP	—	—
10	F	77	L	TIA	AF	16 months	9/92	MIH	VP	1·15	(6/94)
11	M	68	L	TIA	AF	5 months	11/93	MIH	Exc, SVG	0·38	(10/94)
12	M	63	L	TIA	AF	9 months	10/94	MIH	Exc, SVG	0·67	(11/94)

AF, amaurosis fugax; Ath, atheroma; End, endarterectomy; MIH, myointimal hyperplasia; Throm, thrombosis; VP, vein patch; Calc, calcification; CVA, cerebrovascular accident; Ulc, ulceration, TIA, transient ischaemic attack; Exc, carotid artery excision, SVG, saphenous vein interposition graft

injury[135,136] has been shown to provide a matrix of cytokines, chemoattractants and growth factors[137–140] into which smooth muscle cells can proliferate. The final result is a mass that narrows the arterial lumen.

Adaptation and remodelling

Blood flow and blood pressure are primary determinants of the arterial lumen diameter and wall thickness. Increases in shear stress stimulate arteries to dilate[141,142]. This occurs when an arteriovenous fistula is created. Increases in tangential wall tension, caused by hypertension, result in thickening of the arterial wall[143]. These adaptive changes are a normal response to altered haemodynamic forces but remodelling may also occur in response to an atherogenic stimulus. As atherosclerotic plaques develop the vessel wall dilates but as the plaque increases in thickness this response fails and a stenosis is formed. This phenomenon has been observed in both human carotid[144] and coronary[145] arteries. Investigators have suggested that failure of this process of adaptation may lead to restenosis[146,147]. Self-expanding intra-arterial stents have been developed in an attempt to reduce recoil and prevent late undesirable remodelling[148].

Animal models

Restenosis can be subdivided into three components: myointimal hyperplasia[149], mural thrombosis[117] and vascular remodelling[150]. Study of each of these components in isolation using an animal model may provide useful information on each individual mechanism but, in order to study the complete process, an 'ideal' animal model should incorporate all three possibilities. Models in which an experimentally induced atherosclerotic vessel is angioplastied most closely resemble human restenosis[151–156].

Pharmacological agents have often been shown to inhibit restenosis in animal models[157–161] but these drugs have failed to produce similar benefits in patients[162–167]. Several reasons have been put forward to explain this discrepancy. Doses used in animal studies are usually between three and 40 times higher than those used in clinical trials. Many of the drugs that are used are also hypotensive agents and may exert some of their effects by reducing blood pressure. Human restenotic tissue has a low index of proliferation in contrast to injured animal tissue. Restenosis can be quantified on perfusion fixed animal tissue whereas angiographic endpoints are open to considerable misinterpretation. Agents should be targeted against all the mechanisms of restenosis and not just against a single component such as intimal hyperplasia if they are to be effective.

Growth factors

Growth factors and the interactions between them are central to the process of restenosis[168] (and atherogenesis) through their effects on smooth muscle cell proliferation and migration, matrix production and vascular remodelling. These cytokines are also responsible for normal healing processes after arterial injury. Many studies on the pathogenesis of restenosis have failed to separate the normal process of vascular healing from the pathological changes of restenosis. Many new strategies against restenosis may also affect vascular healing.

Platelet-derived growth factor. Platelet-derived growth factor (PDGF) was discovered in 1974 and is released by activated platelets[169], endothelial cells[170], vascular smooth muscle cells[171] and activated monocytes. It acts principally by inducing migration of smooth muscle cells[172] for which it is also mitogenic[173]. It is a chemotactic agent for monocytes and neutrophils. Mesenchymal cells increase their synthesis of collagen and increase the activity of interstitial collagenases in response to PDGF. Neointimal formation has been reduced by an antibody to PDGF after carotid de-endothelialization in nude rats[174].

Basic fibroblast growth factor. Basic fibroblast growth factor (bFGF) was discovered in 1939 and is present in vascular smooth muscle cells[175]. It is a potent smooth muscle cell mitogen, and a stimulator of angiogenesis[176]. It can also stimulate endothelial cell regrowth[177]. It has no signal sequence and can be released only if cellular disruption occurs. The extent of smooth muscle cell injury is directly related to the degree of intimal hyperplasia[178]. Systemic injection of a neutralizing antibody against bFGF before balloon catheter de-endothelialization in rats has markedly reduced smooth muscle cell proliferation[179]. Infusion of bFGF has induced smooth muscle cell proliferation in injured rat carotid arteries[178].

Transforming growth factor β Transforming growth factor (TGF) β was first isolated from human platelets in 1978. It is released from platelets, endothelial cells, vascular smooth muscle cells and fibroblasts as an inactive complex called latent TGF-β. Conversion to active TGF-β involves the protease plasmin. TGF-β has a role in smooth muscle cell proliferation and migration[180]; however, it is a very effective promoter of extracellular matrix production[181]. TGF-β has been proposed as a significant growth hormone in the repair of vascular injury and restenosis after balloon angioplasty[182].

Regression or improvement

The early stenotic lesion, developing within the first few months after carotid endarterectomy, has the potential to improve, remain stable or deteriorate. Regression of postoperative carotid stenosis has been observed using serial angiography[183,184]. Resolution of injury-induced lipid-containing intimal lesions has also been demonstrated in an experimental model[185].

The introduction of duplex scanning has provided clearer evidence of regression. Zierler *et al.*[21] serially scanned 22 restenosed arteries and observed regression in nine. Since this initial study others have shown that regression occurs less frequently; values of 1·4 per cent[49], 2·5 per cent[48], 4·8 per cent[32], 10 per cent[26], 22 per cent[51] and 27 per cent[55] have been published. Healy *et al.*[50], using life-table analysis, estimated that there was a 31 per cent cumulative incidence of restenosis at 7 years with a 10 per cent cumulative incidence of regression. No specific factors were identified that could predict regression, and stenoses that did not regress tended to remain stable. Progression of recurrent stenosis was rare and none of the postoperative occlusions was obviously caused by restenosis[50].

Two mechanisms have been postulated to account for regression: first, an adaptive response of the arterial wall to new haemodynamic conditions which occurs typically after the initial proliferative phase and is a feature of remodelling[50,186]; and, second, a reduction of the intimal mass by the organization and resolution of mural thrombosis[51].

Management

The symptomless patient

The outcome of patients with symptomless primary carotid stenosis has been investigated by the ACAS group[187] and the Asymptomatic Carotid Surgery Trial[6]. Symptomless patients with a greater than 75 per cent carotid stenosis have an annual ipsilateral ischaemic stroke rate of only 2·5–3 per cent and a 4–8 per cent annual chance of a vascular death (usually cardiac). Despite these findings, some have concluded that carotid surgery might be justified in these patients[188], although the cost for each stroke prevented is very high. Similar conclusions cannot be inferred in patients with recurrent carotid stenosis. The risk of a patient with a severe recurrent stenosis developing symptoms can be calculated from a number of major reviews (*Table 1*). Symptoms, including stroke, occur in between 8 and 25 per cent, and there is an overall perioperative stroke risk of 3·9 per cent (*Table 3*) in patients who have reoperations.

Table 3 Stroke and operative mortality rates following revisional carotid surgery

Reference	Year	No. of arteries	Mortality rate (%)	Stroke rate (%)
Clagett *et al* [86]	1983	29	3	3
Das *et al* [29]	1985	65	3	2
Piepgras *et al.*[35]	1987	57	0	10
Bartlett *et al.*[189]	1987	116	1·7	2·6
Kazmers *et al* [190]	1988	14	0	0
Bernstein *et al.*[49]	1990	10	0	0
Trieman *et al.*[191]	1992	162	0·2	0·9
AbuRahma *et al* [63]	1994	46	0	7
Lattimer *et al.*[67]	1996	12	0	8
Total		511	1·0	3·9

Bernstein *et al.*[49] followed 484 carotid endarterectomies with serial duplex scans performed at 3 days, 1, 3, 6 and 12 months, and annually thereafter to address the effect of carotid restenosis on symptoms, stroke and death. Life-table analysis up to 10 years revealed a significantly greater life expectancy among those with restenosis. When survival, neurological symptoms and stroke were all taken as endpoints, the likelihood of patients with a recurrent stenosis greater than 50 per cent remaining alive, symptom- and stroke-free, was also greater than that in patients without a stenosis.

Ackroyd *et al.*[192] demonstrated a significant association between contralateral disease progression and the development of symptoms. Others have confirmed this relationship[193,194]. Cook *et al.*[57] and others[195] concluded that routine duplex examination after carotid endarterectomy was probably of little benefit as patients with important disease would develop new symptoms before they had a major stroke.

Hunter *et al.*[40] performed 33 procedures for recurrent carotid stenosis and, on the basis of the macroscopic appearances and histology, concluded that an embolic event rather than reduced blood flow from progressive stenosis was usually the cause of symptoms. The source of the emboli was thought to have been identified on histology in 67 per cent of patients with fibrointimal hyperplasia and in 63 per cent of those with recurrent atheroma. Shanik *et al.*[25] found that patients without a recurrent stenosis developed symptoms more often than those with a restenosis.

The possibility that high-grade carotid stenoses may progress to carotid occlusion has led several units to operate on symptomless patients[19,26,35,61]. Healy *et al.*[50] recognized six late occlusions in a series of 301 carotid endarterectomies, but none developed in patients known to have a severe stenosis. The incidence of ischaemic events and stroke was similar in patients with or without a greater than 50 per cent restenosis. This has been confirmed by others[32].

Despite this clear evidence that further surgery on patients with symptomless carotid stenosis is not indicated. many surgeons in North America still advocate aggressive treatment (*Table 1*). Western Europe has, in general, adopted a more conservative approach than the USA. Universal duplex surveillance following carotid endarterectomy should identify enough patients with symptomless restenosis to enrol patients in a prospective randomized trial to test the belief that a symptomless recurrent stenosis does not require further surgery.

Surgical management

The surgical technique used to correct recurrent carotid stenosis remains a matter of personal choice because only limited and anecdotal experience has been published. The following approaches have been used: endarterectomy alone; saphenous vein[56], PTFE patch[45] or Dacron patch[86] alone; endarterectomy with patching[63]; excision with graft interposition using saphenous vein[196], basilic vein[191], Dacron[189], PTFE[48], bovine artery[191], hypogastric artery[189] or superficial femoral artery[191]; and saphenous vein bypass[37,45].

Table 3 summarizes the literature on the surgical repair of recurrent stenosis. Piepgras *et al.*[35] reported four major and two minor strokes (11 per cent) associated with 57 repairs, a morbidity rate that was four times higher than that for primary carotid operations in the same institution. These authors recommend onlay patch grafting without endarterectomy in patients with myointimal hyperplasia, endarterectomy with patch grafting in patients with recurrent atherosclerosis, and interposition grafts in patients whose vessels are damaged extensively by the recurrent lesion or when acute thrombus is present. The Piepgras series contained 35 recurrent lesions with intraluminal thrombus or caseous material. The increased operative morbidity rate was attributed to thromboembolic complications, believed to result from the increased manipulation required to dissect the carotid bifurcation out of scar tissue.

A recommendation that bypass grafting should be used in the presence of unexplained thrombus is made by others[37] who have advocated that this approach eliminates the previously endarterectomized area and reduces the risk of further thrombosis. Bartlett *et al.*[189] reported five strokes associated with 116 operations (4·3 per cent), resulting in two deaths. Twenty-three cranial nerve palsies occurred: 12 hypoglossal, seven of the mandibular branch of the facial nerve and four vagal. Most of these resolved by 3 months. Trieman and colleagues[191] and Bartlett *et al.*[189] reported their experiences in 20 and 12 patients respectively who required operation for recurrent carotid stenosis. Resection and graft interposition was considered to be the treatment of choice[189]. AbuRahma *et al.*[63] have reported a tertiary revisional endarterectomy; their patient unfortunately sustained a postoperative stroke.

Angioplasty

Transluminal angioplasty has been proposed as a safer alternative to surgery for recurrent carotid stenosis[197–199]. Bergeon *et al.*[200] attempted to dilate nine recurrent stenoses. Two could not be dilated effectively and two patients developed recurrent restenosis after the procedure. Three patients with proximal lesions all developed neurological complications (two arteries dissected). One of the six patients with distal restenosis developed a hemiplegia which lasted for 24 h. In one patient whose angioplasty restenosed after 6 months a Palmaz stent was deployed across the lesion. There are, however, already anecdotal reports of restenosis occurring after stent deployment.

Intraoperative angioplasty under local anaesthetic with the common carotid bifurcation exposed and under surgical control has been advocated as a safer alternative to percutaneous angioplasty in patients with recurrent stenosis[201]. The combined approach allows backbleeding from the internal carotid artery to wash out potential debris at the completion of angioplasty.

Balloon angioplasty for primary carotid stenosis remains an experimental procedure[202]. Although there are at least four patients in the CAVATAS who have undergone successful carotid dilatation for restenosis, the follow-up interval is short and the number of patients eventually required to demonstrate a significant benefit over surgery could never be achieved. This approach should be reserved for surgically inaccessible lesions or kept within the confines of a trial until there is more evidence that the technique is safe and effective.

Pharmacology

Aspirin. Five randomized prospective trials[203–207] have demonstrated that platelet antiaggregants like aspirin, if given to patients after carotid endarterectomy, produce only a marginal benefit in reducing neurological complications. Patient survival, however, seems to be prolonged because of a reduction in the number of cardiac deaths and vascular events in general[203,208]. Several studies have failed to demonstrate that aspirin has any benefit in reducing recurrent carotid stenosis[86,206,209]. Sze *et al.*[210], in a meta-analysis of several randomized controlled trials, failed to demonstrate that antiplatelet agents are of any value in cerebrovascular disease. Although antiplatelet drugs have no proven benefit in reducing restenosis, their use after surgery is recommended because of their properties of increasing survival and reducing postoperative transient ischaemic attacks.

Anticoagulants. Meta-analysis has failed to show that anticoagulant therapy prevents cerebrovascular disease[211]. As with aspirin, myocardial infarction and reinfarction appear to be reduced and patient survival is improved[212,213]. The danger of cerebral haemorrhage may make long-term anticoagulant therapy undesirable, although this risk may be overestimated[214].

Experimental agents. Many pharmacological agents have successively reduced intimal hyperplasia in an experimental situation. These include fish oils[215], antiproliferative drugs[216], prazosin[217], steroids[218], nitric oxide agonists[219], nitric oxide donors[220] and gene therapy[221,222]. Unfortunately, all these agents remain unproven in humans and the results of prospective clinical studies are awaited.

Local drug delivery. Topical or local administration of agents against restenosis has many theoretical attractions; however, the immediate restoration of the circulation after the procedure is a major drawback in terms of the time available for them to act. Many novel strategies have been developed to increase the contact time of the active drug. Hydrogel-coated angioplasty balloon catheters are capable of absorbing and delivering a wide range of biological agents[223,224]. Infusion balloon catheters have the capability to deliver drugs through small perforations in the balloon[225]. Antisense oligonucleotides can also be delivered directly to the arterial wall by two methods, direct application of a gel matrix containing phosphorothioate-modified oligonucleotide to the adventitial surface[226] and intraluminal installation with interruption of blood flow by complexing the oligonucleotide with a virus transport liposome[227]. Bioabsorbable stents may soon be available which maintain lumen calibre while releasing biologically active agents. Photodynamic therapy has recently been shown to reduce experimentally induced intimal hyperplasia by targeting the action of various photosensitive agents to the site of catheter injury[228].

Conclusions

Carotid endarterectomy is an established and effective operation with a low incidence of symptomatic recurrent stenosis (0–8·2 per cent). Symptomless recurrence is, however, much more common (1·3–37 per cent); it usually has a benign course and may regress. Histology of the excised narrowing usually reveals myointimal hyperplasia within the first 2 years and recurrent atherosclerosis therafter. Macroscopic examination of the surface of symptomatic stenoses usually reveals areas of thrombosis, ulceration or friability, which may well cause embolic events. Intraoperative assessment of carotid endarterectomy by completion angiography and duplex scanning demonstrates that recurrent stenosis may occur in arteries that have had near perfect operations, although there is some evidence that a poor technical result may predispose to early and more severe narrowing. The use of a vein patch, shunt or tacking sutures does not appear to have any effect on restenosis. Similarly, there is no clear association with smoking, hypertension, diabetes, hyperlipidaemia, or male or female sex.

Many operations have been advocated to treat recurrent stenosis but there is limited experience at most centres and the nature of the evidence is anecdotal. A previously endarterectomized artery heavily infiltrated with atheroma, or an artery in which a sharp dissection plane is difficult to find because of severe myointimal hyperplasia, is probably best replaced with an autologous interposition or prosthetic graft. Patch angioplasty or repeat endarterectomy with or without patch angioplasty is acceptable in other circumstances. The use of a shunt is recommended in all patients because a repeat procedure is usually more difficult and takes longer to perform than a primary operation.

Patients requiring a revisional operation are at present still rare. They are more likely to have symptoms from an unoperated contralateral bifurcation or to develop unrelated transient neurological symptoms. Symptomless carotid restenoses do not require surgery until a clinical trial demonstrates a clear benefit in terms of patient survival or stroke reduction. The indications for revisional surgery on symptomatic recurrent carotid stenosis should be the same as those for the original operation, with the understanding by both surgeon and patient that the secondary operation is more difficult, and the complications of stroke, transient neurological events and cranial nerve palsies are increased.

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Surgical practice is evidence based

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Background The quality of surgical research, and particularly the reluctance of surgeons to perform randomized controlled trials, has been criticized. The proportion of surgical treatments supported by satisfactory scientific evidence has not been evaluated previously.

Methods A 1-month prospective audit was performed of 100 surgical inpatients admitted under two consultants in a general surgical/vascular unit at an urban teaching hospital; the main illness and interventions were agreed through group discussions in each case. The literature concerning the efficacy of each treatment was reviewed, and the evidence was categorized as: (1) supported by randomized controlled trial evidence; (2) sufficient other evidence of efficacy to make a placebo-controlled trial unethical; or (3) neither of the above.

Results Of the 100 patients studied, 95 (95 per cent confidence interval (c.i.) 89–98) received treatment based on satisfactory evidence (categories 1 and 2) and, of these, 24 patients (95 per cent c.i. 17–35) received treatments based on randomized controlled trial evidence and 71 had treatments based on other convincing evidence (95 per cent c.i. 62–80).

Conclusion Inpatient general surgery is 'evidence based', but the proportion of surgical treatments supported by randomized controlled trial evidence is much smaller than that found in general medicine. Some reasons for this are clear, but the extent to which surgical practice needs to be re-evaluated is not. Current methods for classifying and describing evidence in therapeutic studies need improvement.

The extent to which current clinical practice is supported by satisfactory scientific evidence is currently under investigation. A system for evaluating this evidence has been proposed, and has been termed evidence-based medicine[1]. Initial estimates suggested that fewer than 15 per cent of medical interventions were evidence based, but a recent study showed that 82 per cent of the principal treatments carried out in a UK general medical ward were based on satisfactory evidence[2]. Because the majority of modern surgical operations have their origin in the late nineteenth and early twentieth centuries, there is reason for concern that the evidence base for current surgical practice might be less satisfactory. Recent criticism of the quality of surgical research has suggested that surgeons are particularly unwilling to perform randomized controlled trials (RCTs)[3], and the proportion of surgical treatments that are based on such trials, or on other forms of satisfactory evidence, is not known.

Current financial and political pressures to reduce healthcare costs mean that any intervention that cannot be justified as soundly based is potentially liable to restriction or abolition by healthcare purchasers. The authors therefore decided to carry out a study of practice in general surgery to determine how much of the activity in this specialty is evidence based.

Patients and methods

Patient population

The patients studied were all general surgical inpatients admitted under the care of two consultant surgeons at Fazakerley Hospital, Liverpool, during September 1995. Elective and emergency patients were included. Patients admitted for elective day-case surgery were included if they attended the main general surgical unit, but not if they were admitted to the day-case unit which is presently situated in a different hospital. Patients who were already in hospital on 1 September 1995 were excluded. Those who attended the hospital as an emergency and had a surgical consultation were not included unless they were formally admitted by the surgical team for inpatient care. Patient management was carried out entirely according to normal local practice, and no attempt was made to define the evidence base for the treatments used until after treatment had been selected and carried out.

Literature searching methods

In each case included in the study the main diagnosis and main treatment were defined by agreement in the study team. A literature search was then carried out to identify evidence supporting the efficacy of this treatment for the condition diagnosed. The principal sources searched were: (1) Medline database of *Index Medicus* 1968–1995; (2) references from surgical texts in the Harold Cohen Library, University of Liverpool, and the library of the Liverpool Medical Institution; (3) texts of the history of surgery; (4) specific questioning of local consultants with a special interest in the area of surgery concerned, and (5) review of the list of treatments and their categorization by four selected academic surgeons.

Assignation of treatments to categories

Following data collection, meetings of the study group took place to discuss the evidence found to support each intervention identified. This group comprised the four authors of this paper (one consultant/senior lecturer, one lecturer and two surgical senior house officers). The study group therefore included one of the consultants under whose care the patients were admitted, but excluded the other. After the study group had completed its deliberations, a consultant general surgeon from the same hospital trust, who took no part in the study, was asked to review the list of primary diagnoses and treatments, and to grade them independently with the assistance of relevant publications found

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by the review group members. Treatments were placed into one of three categories based on the results of these discussions, as suggested by Ellis *et al.*[2] Category 1 treatments are supported as effective by a well conducted RCT Category 2 interventions are those for which no RCT evidence exists, but where there is sufficient other evidence to convince all members of the study group that to conduct a randomized trial would be unnecessary, or, if the comparison was against placebo or no treatment, unethical These two categories are considered to be evidence based. Category 3 comprises the remaining treatments, which did not meet the criteria for inclusion in either of the other two categories. Exact confidence intervals were calculated on proportions assuming a Poisson distribution.

Results

Exactly 100 patients were admitted to the two consultant firms during the month of the study. *Fig. 1* illustrates the overall distribution of evidence supporting treatment choice. Some 24 patients (95 per cent confidence interval (c.i.) 17–35) were given treatments supported by RCT evidence (category 1), 71 (95 per cent c.i. 62–80) were treated by methods supported by other forms of evidence (category 2) and only five received treatment for which no satisfactory supportive evidence could be found (category 3). The independent reviewer agreed with these assignments in all cases. By the criteria defined in this study, 95 per cent (95 per cent c.i. 89–98) of surgical treatments were deemed to be evidence based. All five patients in category 3 received non-operative emergency treatment, in a total of 34 patients who received such

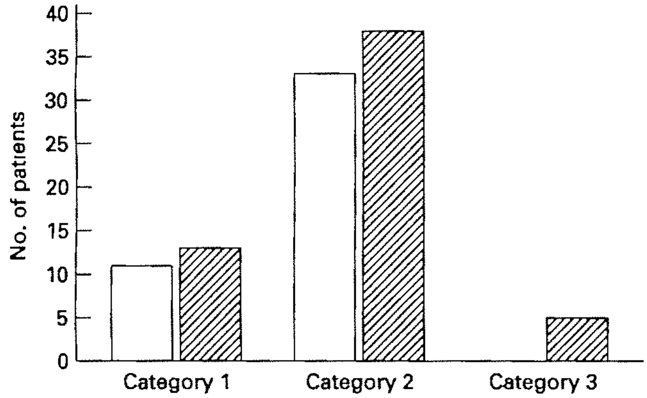

Fig. 1. Cases classified by category of evidence supporting the choice of treatment given· category 1, randomized clinical trial (RCT) evidence in favour of treatment; category 2, convincing non-RCT evidence for treatment; category 3, neither of these. □, Elective treatment; ▨, emergency treatment

Table 1 Evidence supporting 44 elective operations performed by the study group, for the diagnoses agreed on

Diagnosis	Treatment	*n*	Evidence
Benign skin lesion	Local anaesthesia and excision	10	2
Mammographic lesion	Wire-guided biopsy	4	2
Breast lump	Excision biopsy	3	2
Breast cancer and ductal carcinoma *in situ*	Mastectomy	1	2
Gallstones	Laparoscopic cholecystectomy	3	1[4,5]
	Open cholecystectomy	2	2
Inguinal hernia	Lichtenstein repair	3	2
Incisional hernia	Mesh repair	3	2
Haemorrhoids	Haemorrhoidectomy	1	1[6]
Anal fissure	Lateral sphincterotomy	2	1[7]
Fistula *in ano*	Examination under anaesthesia and fistulotomy	1	2
Colostomy	Closure	1	2
Rectovaginal fistula	Anterior resection	1	2
Peripheral vascular disease	Bypass grafting	2	2
Varicose veins	High ligation and stripping	5	1[8]
Gastric cancer	Staging laparoscopy	1	2
Gastric cancer	Gastrectomy	1	2

Table 2 Evidence supporting 22 emergency operations performed by the study group, for the diagnoses agreed on

Diagnosis	Treatment	*n*	Evidence
Appendicitis	Appendicectomy	6	1[9]
Perforated diverticular disease	Hartmann's operation	1	2
Rectal prolapse	Delorme's operation	1	2
Strangulated hernia	Repair	2	2
Critical limb ischaemia	Bypass grafting	2	2
Gallstones	Delayed laparoscopic cholecystectomy	3	1[4,5]
Thrombosed haemorrhoids	Haemorrhoidectomy	2	1[10]
Lower limb gangrene	Amputation	2	2
Ischaemia of right hand	Exploration of brachial artery	1	2
Abscess	Incision and drainage	2	2

Table 3 Evidence supporting 34 emergency non-surgical treatments administered by the study group, for the diagnoses agreed on

Diagnosis	Treatment	*n*	Evidence
Urological			
Urinary tract infection	Antibiotics	3	2
Acute retention	Urethral catheter	4	2
Epididymo-orchitis	Antibiotics	3	2
Gastrointestinal			
Adhesion obstruction	Conservative	3	2
Non-specific abdominal pain	Observation	4	3
Diverticulitis	Conservative	1	2
Acute pancreatitis	Conservative	1	2
Antibiotic diarrhoea	Intravenous rehydration	1	2
Exacerbation of peptic ulcer	H_2 antagonist	1	2
Constipation	Enemas and laxatives	1	2
Oesophagitis	Omeprazole	1	1[11]
Irritable bowel syndrome	Mebeverine	1	1[12]
Gastric volvulus	Conservative	1	3
Trauma			
Head injury	Observation	1	2
Splenic haematoma	Conservative	1	2
Blunt liver trauma	Conservative	1	2
Stab wound to chest	Chest drain	1	2
Miscellaneous			
Gallstones and jaundice	ERCP and ES	2	2
Metastatic cancer	Palliative care	2	2
Lung abscess	Antibiotics	1	2

ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy treatments. *Tables 1–3* give details of the diagnoses and treatments of all patients in the study.

Discussion

The idea that clinical practice should be rigorously based on the best scientific evidence is not new[13], but the recent reformulation of the concept by Sackett *et al.*[14] has proved useful in stimulating thought and debate. As Sackett and colleagues pointed out[14], it is important in applying the evidence-based approach to avoid the twin pitfalls of hastily rejecting the unproven and of creating a straightjacket of protocol-driven medicine. Continual self-questioning over the justification for practices is an unquestionable professional duty for all doctors, and the systematic approach to reviewing and classifying the literature provided by evidence-based medicine can only be helpful in this regard.

Of the surgical interventions studied, 95 per cent were judged to be evidence based. This value is slightly higher than the proportion (82 per cent) of general medical treatments previously categorized as evidence based[2]. The proportion of surgical interventions based on RCT evidence (24 per cent) was, however, less than half that previously found in general medicine (53 per cent)[2]. The results relate only to inpatient general surgery, as day cases were excluded from this study. The authors considered that the large throughput of these minor cases could distort the overall result as a figure of relevance to the practice of surgery, and that they were best dealt with separately. It is accepted that the evidence supporting day-case treatments has not been evaluated, including evidence to support the treatments being given as day cases rather than on an inpatient basis.

The authors are uneasy about the comfortingly high overall percentage of evidence-based treatments because of the very variable quality of the evidence supporting treatments in category 2. The definition used for this category was the same as that used by Ellis *et al.*[2], and in the present authors' view it is seriously flawed. The judgements as to whether the intervention could be ethically compared with placebo were subjective, and were made by the same individuals who treated the patients. If surgeons were thought likely to believe particularly strongly in established treatments, in the absence of clear scientific evidence to support them, this result might be predicted. This methodological weakness leaves some doubt as to the meaning and value of the term 'evidence based' when it is founded on this definition.

Why should the proportion of RCT-based treatments be so much lower in surgery than in medicine? A number of factors other than surgical attitudes may have contributed to this difference. The elective workload was influenced by the interests of the two consultants (surgical oncology and vascular surgery), and a different elective profile might produce somewhat different results, but only 13 of the 100 patients were clearly 'specialty' cases. Many surgical treatments are long established, while most effective drugs available to physicians have been introduced during the past 30–40 years. This period of pharmacological innovation has paralleled the establishment of the randomized controlled clinical trial as the standard experimental method in therapeutic research. Randomized trials become difficult after a treatment has become established practice because of lack of physician equipoise, and this applies to old medical treatments just as much as to old operations. The importance of adequate funding for RCTs should also be considered. Funding of large multicentre surgical RCTs by national bodies or commercial interests is rare, and the knowledge that such funding is unlikely may discourage surgeons from attempting large trials. The practical difficulties of conducting a satisfactory RCT of a surgical procedure are much greater than those encountered with most medical treatments. Standardization of a complex surgical procedure, unlike the standard administration of most drug regimens, is a major challenge. If one of the techniques under study is new, the participating surgeons may experience a substantial learning curve before reaching a steady level of performance[15]. Even after this, performance between surgeons is likely to vary quite widely[16]. Modification of the technique in response to particular circumstances in individual patients may appear necessary to the surgeon in a significant proportion of cases. Elimination of such cases from the study would be likely to introduce serious bias as well as increasing recruitment problems. Conversely, inclusion of all randomized patients on an 'intention to treat' basis can result in the inclusion of a large proportion of patients in each treatment group who did not receive the proposed operation, as occurred in a recent carefully designed comparison of two surgical techniques[17]. Patient preference and clinical equipoise often pose problems in comparisons between a surgical and a non-surgical treatment, or two very different operations. Finally, the relative rarity of some serious surgical conditions would make recruitment of adequate numbers difficult even if many centres were involved. A recent estimate, based on apparently realistic assumptions, suggested that only 39 per cent of surgical treatments could be subjected to RCT under ideal conditions[18].

If the majority of surgical treatments cannot be subjected to RCT, it will be necessary to develop better methods of categorizing the non-RCT evidence supporting treatment choices. Much work has been done on evaluating the quality of RCTs[19–21], but the evaluation of quality in non-RCT studies has proved more difficult. A number of general classifications of evidence more complex than that of Ellis *et al.*[2] are in current use, but the present authors are not aware of any that are both practical and objectively validated. There have been few statistical studies of the relative reliability in practice of RCTs and other study methods, but the findings in one analysis of surgical publications did not suggest that other study methods were always so inferior as to be unworthy of consideration[22]. If both RCT and non-RCT studies could be reproducibly scored for quality on the same scale, it would be easier to evaluate the reliability of existing evidence. The authors believe that this more detailed analysis of the quality of available evidence is essential for the further progress of evidence-based medicine as a useful tool to influence clinical practice, and studies have been commenced to determine how this could be achieved.

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Addendum

The Sheffield study of laparoscopic cholecystectomy *versus* mini-cholecystectomy[23] was published after completion of this study. This important new evidence was not available to the clinicians making decisions on the patients described, and has not, therefore, been included. The study group consider that inclusion of the data in this paper would have had the effect of moving six cases from category 1 to category 2. The proportion of all cases would therefore be altered to 18 per cent in category 1 and to 77 per cent in category 2

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Postoperative choledochoscopic removal of intrahepatic stones via a T tube tract

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Background The management of primary intrahepatic stones is extremely difficult. During operation it is often difficult to remove all the stones. The postoperative T tube tract provides an invaluable access to the intrahepatic system.

Methods This paper reports a retrospective review of postoperative choledochoscopic removal of intrahepatic stones in a series of 44 patients. Special emphasis is placed on the result of the procedure and on the long-term outcome of patients.

Results Overall, the procedure was successful in 22 of the 44 patients. Presence of strictures was associated significantly with failure rate ($P = 0.002$). There were complications in five patients; most subsided with conservative management. However, there was one procedure-related death in the series. Some 28 patients were followed for 16–115 months. The long-term outcome was significantly related to the success rate of choledochoscopic stone removal ($P = 0.03$).

Conclusion All intrahepatic stones should be removed. T tube choledochoscopy is the preferred method for treating retained intrahepatic stones. This should be supplemented with other modalities of treatment, such as endoscopic and radiological approaches, especially in patients with strictures.

The management of primary intrahepatic stones is extremely complex – very difficult but challenging. With the advent of biliary endoscopy, operative exploration of the bile duct has decreased dramatically, yet the problem of residual stones remains. The reported incidence of residual stones in patients with intrahepatic stones is very high, between 54 and 71 per cent[1]. In the operative treatment of intrahepatic stones, it is often difficult to remove all the stones. The postoperative T tube tract provides an invaluable access to the intrahepatic system. A flexible choledochoscope was first used by Nakamura *et al.*[2] to remove residual stones. This was followed by reports of its use for intrahepatic stones, and the success rate varied from 82 to 96 per cent[3–7]. This study presents 44 patients with residual intrahepatic stones who underwent postoperative choledochoscopy. Special emphasis is placed on the result of the procedure and on the long-term outcome of patients.

Patients and methods

Between January 1986 and December 1992, postoperative choledochoscopy via the T tube tract was performed in 83 patients who had undergone exploration of the common bile duct in the Department of Surgery, Queen Elizabeth Hospital, Hong Kong. Some 44 patients had intrahepatic stones, both with and without concomitant extrahepatic stones, and 35 had extrahepatic stones only. Choledochoscopy was performed in four patients for solely diagnostic purposes. A retrospective study was undertaken to analyse the results and complications of the procedure, as well as the long-term outcome of patients with intrahepatic stones. Among the 44 patients with intrahepatic stones, there were 25 women. Age ranged from 28 to 80 (mean 59·5) years. All the patients in this series had had previous open exploration of the common bile duct; 39 explorations were performed during emergency operation. At the close of the operation, a T tube was brought out from the common bile duct, usually at a convenient site. Two patients had choledochojejunostomy performed and the T tube was brought out from the upper end of the common bile duct. There was no liver resection in this series.

Some 6 weeks after the initial operation, the T tube tract was serially dilated with a set of coaxial metal dilators, then splinted with a 24-Fr Silastic T tube (Dow Corning, Tokyo, Japan). After dilatation, the tract was rendered straight with a diameter of 8 mm. A few days later, a flexible choledochoscope (Olympus CHF-T20; Olympus, Tokyo, Japan) with an outer diameter of 6 mm could be inserted via the dilated tract into the biliary system. All procedures were performed under intravenous sedation.

Stones were removed by a variety of wire baskets, tripods and Fogarty balloons Larger stones were fragmented by electrohydraulic lithotripsy (Riwolith; Wolf, Knittlingen, Germany) which has been available in the author's department since 1990. Strictures were dilated with balloon dilators. Some difficult cases required selective cholangiography during choledochoscopy to outline the peripheral branches and locate stones beyond a stricture. At the end of the procedure, the tract was again splinted with a Silastic T tube. The procedure was repeated every 3–7 days when necessary, until all stones had been cleared as ascertained by choledochoscopic examination. Cholangiography was further performed to confirm the clearance (*Fig. 1*). In the more complicated cases in the latter part of the series, non-contrast-enhanced computed tomography (CT) was also performed to help detect any residual stones.

Patients were followed regularly after operation Symptoms were assessed using a standardized symptom score. The results of the procedure and of long-term outcome were categorized into two groups for statistical analysis. The χ^2 test was used to compare the difference in proportions; the level of significance was taken as $P < 0.05$.

Results

The sites of residual stones were 23 in the left intrahepatic ducts, 12 in the right side and nine bilateral. Seventeen patients had concomitant extrahepatic stones, all of which were completely removed, and 17 had intrahepatic duct strictures. The strictures were dilated with balloon dilators during the procedure. Seven T tube tracts did not need dilatation because a 24-Fr T tube had

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already been inserted during operation in anticipation of residual stones. The tract could not be dilated in two patients because of excessive angulation and disruption of the T tube tract; subsequent choledochoscopic examination was not possible in these patients. A total of 98 choledochoscopic examinations was performed in the remaining 42 patients, with a mean of 2·3 (range 1–12) sessions per patient.

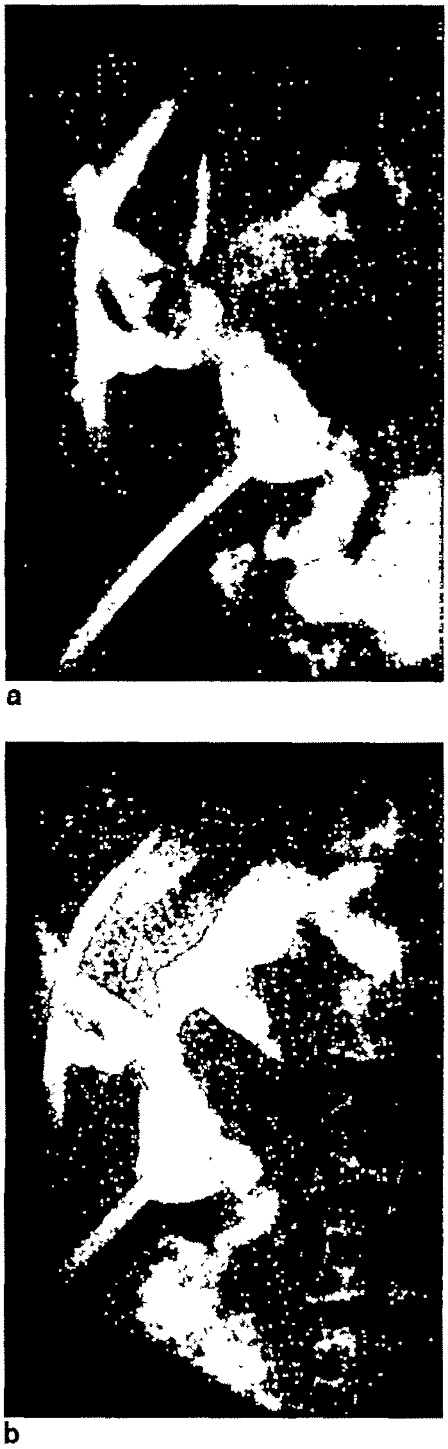

Fig. 1 a Postoperative T tube cholangiogram showing intrahepatic stones. b Stones were removed after multiple choledochoscopic procedures

There were complications in five of the 44 patients, and one patient died. There were two fistulas of the T tube tract after dilatation, one leading into duodenum and one into small bowel. Both of these subsided after conservative treatment; however, further choledochoscopic examination had to be abandoned. A peripheral left intrahepatic duct was perforated during manipulation in one patient. This healed spontaneously. Two patients developed septicaemia after the procedure; infection subsided following antibiotic treatment in one patient, but the other died despite vigorous resuscitation.

Complete removal of the intrahepatic stones was achieved in eight of the 44 patients. Some 14 patients had near-complete removal, implying that all the stones were cleared except those in peripheral branches that could be detected only by CT or selective operative cholangiography. Eleven patients had incomplete removal, although at least half of the stones were removed. In a further 11 patients the procedure was considered a failure, either because the ducts could not be accessed or because less than half of the stones were removed. The procedure was considered a success after complete or near-complete removal, and this was achieved in half of the 44 patients. Those with incomplete removal were considered treatment failures. The causes of failure included failed dilatation of T tube tract in two patients; failed manipulation in 17 patients; and three patients discharged against medical advice. Of all factors related to failure, the presence of strictures was the single most important one (*Table 1*). The presence of right intrahepatic stones did not correlate with failure.

Among the 44 patients, one died and three had an operation immediately after failure of the procedure. Twelve patients defaulted on follow-up or had less than 1 year of follow-up; all were excluded from analysis for long-term outcome. Of the remaining 28 patients, the follow-up period ranged from 16 to 115 (mean 53·2, median 48·5) months. Six patients died during follow-up. One patient died from septicaemia after another operation for cholangitis 16 months later; the other five died from unrelated diseases (lung cancer (two), chest infection (two) and hepatocellular cancer (one)) 35–58 months later. Symptom scores are shown in *Table 2*. Scores of 0–3 were regarded as a favourable outcome and those of 4–6 as unfavourable.

Statistical analysis was based on this categorization. The type of operation performed in those scoring 6 included re-exploration of bile duct (two patients), choledochojejunostomy (four) and segmentectomy (one), 5–54 months later. Long-term outcome was analysed in relation to the success of the choledochoscopic procedure. Patients with symptom scores greater than 3 were as follows: two of six of those with complete removal, two of ten with near-complete removal, five of seven with

Table 1 Presence of stricture compared with result of choledochoscopic procedure in 42 patients*

	Successful procedure	Unsuccessful procedure
No stricture	18	7
Presence of stricture	4	13

*Two patients with failed T tube tract dilatation were excluded. $P = 0{\cdot}002$ (χ^2 test)

Table 2 Symptom score for long-term outcome in 28 patients

Score	Clinical finding	No. of patients
0	Asymptomatic	5
1	Occasional pain	10
2	Frequent pain	1
3	Pain requiring hospital attendance or preventing work	0
4	Occasional admission or cholangitis (fewer than three per year)	4
5	Frequent admission or cholangitis (more than two per year)	1
6	Need for reoperation	7

Table 3 Long-term outcome compared with result of choledochoscopic procedure in 28 patients

	Favourable outcome (score 0–3)	Unfavourable outcome (score 4–6)
Successful procedure	12	4
Unsuccessful procedure	4	8

$P=0{\cdot}03$ (χ^2 test)

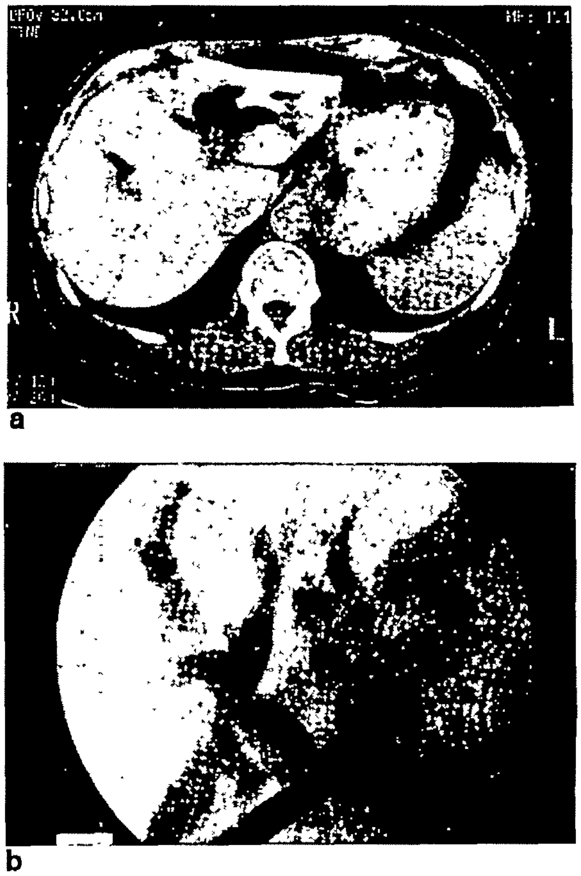

Fig. 2 **a** Computed tomogram showing stones in a peripheral duct. **b** Selective cholangiogram during choledochoscopy

incomplete removal and three of five with failure of choledochoscopy (*Table 3*). The long-term outcome was significantly related to the success of choledochoscopic removal ($P=0{\cdot}03$).

Discussion

The incidence of intrahepatic stones is high in this locality, reaching approximately 15 per cent of patients with calculous disease of the biliary tract. Intrahepatic stones are frequently found in patients with recurrent pyogenic cholangitis[8]. The T tube tract after exploration of the bile duct provides an excellent portal for entry into the intrahepatic ductal system. This allows the passage of a flexible choledochoscope into the bile ducts. Stones can be seen and removed, and strictures can be dilated.

The results from this series were unsatisfactory compared with the success rates reported by Hwang *et al.*[3] (96·1 per cent) and Choi and co-workers[4] (82·3 per cent). However, this was a difficult group of patients to treat, particularly as the majority required emergency operation. Advances in hepatobiliary imaging and interventional techniques could have obviated the need for emergency operation and allowed a planned approach in managing the problem. The mortality rate associated with this procedure is low and the morbidity is acceptable, as shown in the present series as well as in reports from other studies[3–4,6,9–11].

Even though safe, removal of intrahepatic stones is technically difficult. Difficulties are encountered when there are concomitant intrahepatic duct strictures, stones impact in the peripheral branches, or when the entire intrahepatic system is packed with stones. Localization of stones by choledochoscopic examination can be difficult and at times impossible. Stones hidden beyond strictures may not be seen, yet can be numerous. For this reason, the author advocates the use of selective cholangiography during the procedure to locate the stones. The postoperative cholangiogram may not outline a segmental duct because it may be air-filled or packed with stones. Non-contrast-enhanced CT is helpful in this situation to localize residual stones and to document clearance (*Fig. 2*). Therefore, it should be done in difficult and complicated cases. In the present series, the presence of right intrahepatic stones did not contribute to failure. This does not follow the author's original belief that access to the right ductal system is more angulated in relation to the orthodox T tube tract that exits on the right side of the abdominal wall. This can probably be explained by the straightness of the tract achieved after tract dilatation. The manoeuvrability of the tip of the flexible choledochoscope is much enhanced. Previous dilatation of the T tube tract by coaxial dilators probably contributes to success in removal of intrahepatic stones.

Biliary strictures are often encountered during the removal of intrahepatic stones. This was shown to be the single most important factor that accounted for failure in the present study. This has also been reported in other series[3,6]. Multiple strictures in the biliary system make localization of stones extremely difficult. Strictures may be too rigid to dilate; sometimes, even after dilatation, the scope still cannot pass through. The use of a slim choledochoscope, electrohydraulic lithotripsy[12] or laser lithotripsy[13] may improve the success rate. Biliary strictures shown on the cholangiogram should alert the surgeon to the difficulty. Multiple modalities of therapeutic approach have to be considered and planned well beforehand.

Endoscopic sphincterotomy has now been widely accepted in the management of bile duct stones. Clearance of bile duct calculi has been achieved in 87–93 per cent of patients following successful sphincterotomy[14,15]. Difficulties may be encountered with stones inside peripheral branches or in patients with strictures. However, endoscopic sphincterotomy can play an additional role to percutaneous T tube choledochoscopy in facilitating the passage of stone fragments. Percutaneous transhepatic biliary drainage has become another accepted technique, which not only alleviates cholangitis, but can also provide an access for stone removal. Complication rates range from 14·5 to 24 per cent in various series[3,16–18]. When the percutaneous transhepatic approach is combined with surgery, long-term outcome has been reported to be good[19]. Although these figures are encouraging the results and morbidity should be weighed against those of other treatment options. Patients with stones beyond the reach of the T tube choledochoscope, with multiple strictures or with diffuse bilobar involvement appear to be good candidates for the transhepatic route.

Burhenne[20] and Han *et al.*[21] reported successful removal of bile duct calculi under fluoroscopic screening. This technique has largely been replaced by choledochoscopic manoeuvres, but is particularly helpful in negotiating strictures. Intracorporeal electrohydraulic[12,22] or laser[13] lithotripsy was shown to be effective in fragmenting biliary calculi. There have been reports on extracorporeal shockwave lithotripsy (ESWL) of bile duct calculi. The latest report by Meyenberger and colleagues[23] showed that stone disintegration was achieved in 93 per cent but failed in all three patients with intrahepatic stones. The overall complication rate was 7 per cent. ESWL combined with choledochoscopic or radiological techniques can be helpful in achieving stone fragmentation in unfavourable positions or above strictures, thus improving the success rate of T tube choledochoscopy[24].

Surgery for intrahepatic stones has been disappointing. The incidence of recurrent symptoms requiring reoperation after common duct exploration, transhepatic intubation or hepatotomy was 24, 37 and 75 per cent respectively[25]. Cholecystectomy and exploration of bile duct followed by T tube choledochoscopy is the recommended treatment for patients with gallstones and complex ductal stones that cannot be removed by the endoscopic trans-sphincteric route. Hepatic resection to excise the diseased ducts has produced the best results[25,26], although this could be achieved in only 15 per cent of patients. Left lateral segmentectomy is recommended by some authors for left intrahepatic stones with tight proximal strictures[3,17,25]. Choledochojejunostomy with a long subcutaneous Roux loop has been advocated by some authors[27,28]. However, the length of Roux loop is crucial as laxity of the loop hinders choledochoscopic manoeuvres and sometimes the stricture or the anastomosis cannot be accessed. Use of the subcutaneous Roux loop has been abandoned in some institutions[3] as endoscopic and radiological interventions have become widely available.

Follow-up assessment of the present patients has been disappointing, probably related to the prolonged follow-up ranging from 16 to 115 months and the high failure rate. Only 16 of 28 patients had a favourable outcome with a symptom score of less than 4. Although only 28 patients were followed for this period, long-term outcome was found to be significantly related to the success of the previous choledochoscopic procedure. The more complete the removal of the intrahepatic stones, the more likely is the patient to be asymptomatic. All intrahepatic stones should be removed if possible; this may require persistence, especially in patients with stricture.

For complex intrahepatic stones, no single treatment modality has been shown to be effective when applied alone. Percutaneous choledochoscopy via a T tube tract can provide invaluable access to the intrahepatic ductal system, with low morbidity and mortality. This is thus the preferred method for treating retained biliary calculi in patients left with a T tube after operation. However, stones are still difficult to clear in patients with strictures, where a combination of different treatment modalities will be necessary.

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Role of hepatic resection in surgery for bilateral intrahepatic stones

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Background Hepatic resection is the treatment of choice for unilateral intrahepatic stones. The availability of the flexible choledochoscope has greatly changed the management of intrahepatic stones. Little has been reported regarding hepatic resection for bilateral intrahepatic stones.

Methods Fifty-nine (15·1 per cent) of 392 patients with bilateral intrahepatic stones underwent hepatic resection. The indications and results were reported. Surgical outcome and long-term follow-up were analysed, and results were compared with those in patients not undergoing hepatectomy.

Results Fifty-nine patients underwent hepatic resection because of destruction of the left liver by repeated infection ($n = 40$), multiple cholangitic liver abscesses ($n = 18$) or associated intrahepatic cholangiocarcinoma ($n = 1$). The hospital mortality rate was 1·7 per cent. The majority of complications were wound infection (9 per cent), haematobilia (5 per cent) and biliary fistula (3 per cent). The incidence of residual stones after surgery was 60 per cent. One year after postoperative choledochoscopic stone extraction, the rate of complete stone clearance was 84 per cent. In patients who did not have hepatectomy the respective rates were 90·1 and 52·9 per cent. The recurrence rate for stones in the hepatectomy and no-hepatectomy groups was 12 and 33·0 per cent respectively.

Conclusions Compared with patients not undergoing hepatectomy, those having hepatic resection had similar operative risks, fewer residual stones and a low incidence of recurrent stones ($P < 0{\cdot}05$).

Intrahepatic stones are common in Taiwan, with an incidence of 31–51·6 per cent of all patients undergoing surgery for gallstones[1–4]. The main aims of treatment for intrahepatic stones are clearance of stones and elimination of bile stasis. Hepatic resection is an established treatment method for intrahepatic stones. Although the indication for hepatic resection in many of the reported series is unilateral intrahepatic stones[1–10], some patients with bilateral intrahepatic stones present with a shrunken and atrophic left liver. Little information on hepatic resection for bilateral intrahepatic stones has been reported. This report describes the authors' experience with hepatic resection for bilateral intrahepatic stones, with emphasis on the indications for and results of surgery.

Patients and methods

Between January 1978 and June 1990, a total of 1105 patients with intrahepatic stones were treated surgically in this centre, of which 392 patients (35·5 per cent) had bilateral intrahepatic stones[11]. Of these, 333 patients were treated with common bile duct (CBD) exploration and intraoperative choledochoscopy and 59 (15·1 per cent) underwent hepatic resection (*Table 1*). Preoperative investigations included abdominal ultrasonography, computed tomography (CT), endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography and subsequent percutaneous transhepatic cholangio-drainage. The indication for hepatic resection was when a liver segment or lobe was grossly atrophic secondary to repeated infection ($n = 40$). In this situation, strictures or impacted stones were often found at the orifice of segmental bile ducts, leading to biliary obstruction, acute cholangitis and liver abscesses. The shrunken and destroyed liver segments were readily identified by ultrasonography or CT. Liver resection was also indicated when the affected liver segment was involved by multiple cholangitic abscesses, even though the volume of the liver segment was not reduced ($n = 18$), or when a concomitant intrahepatic cholangiocarcinoma was diagnosed ($n = 1$)[12].

Of the 59 patients who underwent hepatic resection, 18 (31 per cent) had had a previous operation before the hepatic resection. Previous treatments were exploration of the CBD (18 patients), cholecystectomy (13) and hepaticostomy (four). Eight patients (14 per cent) had had three or more operations.

Table 1 Clinical features of patients with bilateral intrahepatic stones

	Hepatic resection ($n = 59$)	No hepatic resection ($n = 333$)
Sex ratio (M:F)	21:38	125:208
Mean (range) age (years)	45·5 (24–70)	50·8 (20–76)
Abdominal pain (right upper quadrant and/or epigastric)*	50 (85)	290 (87·1)
Fever, chills*	44 (75)	258 (77·5)
Jaundice*	20 (34)	150 (45·0)
Abdominal tenderness*	38 (64)	253 (76·0)
Leucocytosis (white cell count above 10 000 per mm^3)*	32 (54)	193 (58·0)
Shock*	0 (0)	35 (10·5)†

*Values in parentheses are percentages. †$P = 0{\cdot}009$ (χ^2 test)

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The operative procedures used in the 59 patients who had hepatic resection were left lateral segmentectomy, CBD exploration and intraoperative choledochoscopy in 58 patients with intrahepatic stones and left lobectomy in one with concomitant cholangiocarcinoma. All patients underwent elective surgery Exploration of the CBD was performed in all of the 333 patients who did not have hepatic resection. A T tube was routinely placed in the common duct after exploration, through which postoperative cholangiography and choledochoscopy were performed.

Postoperative complications were monitored carefully. Operative death was defined as that within 30 days of surgery. The causes of death were determined at autopsy or from the medical records. The results in the group of patients having hepatectomy were compared with those in the group not undergoing hepatectomy. The patient with concomitant intrahepatic cholangiocarcinoma was excluded from the study of long-term follow-up for intrahepatic stones

Statistical analysis

Continuous and categorical variables were compared with the Fisher's exact and χ^2 test respectively. Two-tailed unpaired Student's t test was used for comparisons within groups. Data are expressed as mean(s.e.m.). $P<0{\cdot}05$ was considered significant.

Results

Intraoperative bile culture and gross appearance of the liver

Bile cultures obtained during surgery were available in 56 patients who had undergone hepatic resection. Of these, 54 (96 per cent) were positive. The most common bacteria were *Escherichia coli*, *Enterococcus* and *Klebsiella* species.

Table 2 Postoperative complications of bilateral intrahepatic stones

	Hepatic resection ($n=59$)	No hepatic resection ($n=333$)
Wound infection	5 (9)	20 (6·0)
Haemobilia	3 (5)	15 (4·5)
Biliary fistula	2 (3)	5 (1·5)
Intra-abdominal abscess	1 (2)	4 (1·2)
Postoperative cholangitis	1 (2)	10 (3·0)
Residual stones	35 (60)	300 (90·1)

Values in parentheses are percentages. χ^2 and Fisher's exact tests showed no significant differences between the groups

The resected specimens were sectioned. Foci of cholangitic abscesses were found in 15 cases (25 per cent), fibrous sacs containing muds and stones in 40 (68 per cent) and concomitant intrahepatic cholangiocarcinoma in one.

Morbidity and mortality

One patient in the hepatectomy group and three in the no-hepatectomy group died from prolonged sepsis with intra-abdominal abscess followed by adult respiratory distress syndrome within 1 month of surgery. The hospital mortality rate for patients having hepatectomy was 1·7 per cent. Nineteen patients (5·7 per cent) died after operation in the no-hepatectomy group. The causes of death were acute suppurative cholangitis with septic shock in ten patients, hepatic cirrhosis with hepatic failure or bleeding varices in five, cholangiocarcinoma with acute cholangitis in three and intra-abdominal abscess with septic shock in one[13].

Major postoperative complications were wound infection, haemobilia, biliary fistula and postoperative cholangitis (*Table 2*). No difference was found between the hepatectomy and no-hepatectomy groups.

Retained stones and postoperative choledochoscopy

Thirty-five (60 per cent) of 58 patients who underwent hepatic resection had residual stones after surgery. In 34 of these patients the mean(s.d.) postoperative choledochoscopy rate was 1·5(0·8) (range 1–12) sessions (*Table 3*). The other patient did not undergo choledochoscopy because he died before maturation of the T tube tract. Balloon catheter dilatation of the T tube tract was performed in 18 patients. Lithotripsy with electrohydraulic shockwave was carried out in 15, and stone disruption with the neodymium yttrium–aluminium–garnet (NdYAG) laser in two patients. With a combination of different treatment modalities, complete stone clearance was achieved in 49 (84 per cent) of 58 patients (*Table 4*). The reasons for failure were T tube dislodgement while waiting for choledochoscopy (one patient) and failure to identify the orifice of the strictured intrahepatic ducts (eight).

In the no-hepatectomy group, 300 (90·1 per cent) of 333 patients had residual stones. Altogether, 2570 postoperative choledochoscopies were performed on 297 patients, the mean(s.d.) number per patient being 8·8(5·2) (range 2–40). Residual stones were removed completely in 143 patients (48·1 per cent) (*Table 3*); overall, the

Table 3 Results of postoperative choledochoscopy for retained stones

	Hepatic resection ($n=34$)			No hepatic resection ($n=297$)		
Site of retention	No. of patients	Complete stone removal	Success rate (%)	No. of patients	Complete stone removal	Success rate (%)
Common bile duct	2	2		85	82	96
Intrahepatic duct						
Right	25	22		85	42	
Left	3	1		70	36	
Right and left	6	3		142	65	
Total	34	26	76	297	143	48·1*

*$P<0{\cdot}05$ *versus* hepatic resection (χ^2 test)

complete stone clearance rate in patients not having hepatectomy was 52·9 per cent[14–17] (*Table 4*).

When the complete stone clearance rate immediately after operation and at 1 year was compared in patients who had hepatectomy and those who did not, the former group had much better clearances than the latter (40 and 84 per cent *versus* 9·9 and 52·9 per cent respectively; $P < 0{\cdot}05$; χ^2 test). The mean(s.d.) number of postoperative choledochoscopy sessions for patients undergoing hepatic resection was significantly lower than that in the no-hepatectomy group (1·5(0·8) *versus* 8·8(5·2); $P < 0{\cdot}001$, Student's t test).

Long-term follow-up

Eight of the 49 patients who underwent resection and had complete stone clearance had recurrence of symptoms during long-term follow-up (median 40 months). Six (12 per cent) of these patients were demonstrated to have stone recurrence. Further treatment included percutaneous transhepatic cholangioscopy (three patients), endoscopic papillotomy (one) and CBD exploration (two). Of the other two patients, one developed a cholangiocarcinoma 4 years after surgery and the other suffered from oesophageal variceal bleeding secondary to liver cirrhosis 3 years later. In the no-hepatectomy group, 58 (33·0 per cent) of 176 patients experienced recurrent cholangitis and 42 (23·9 per cent) had further surgery.

Table 4 Complete clearance of bilateral intrahepatic stones

	Hepatic resection ($n = 58$)*	No hepatic resection ($n = 333$)
Surgery alone	23 (40)	33 (9·9)†
At 1 year after choledochoscopic stone extraction	26 (45)	143 (42·9)
Total	49 (84)	176 (52·9)†

Values in parentheses are percentages. *Excludes one patient with concomitant cholangiocarcinoma. †$P < 0{\cdot}05$ (χ^2 test)

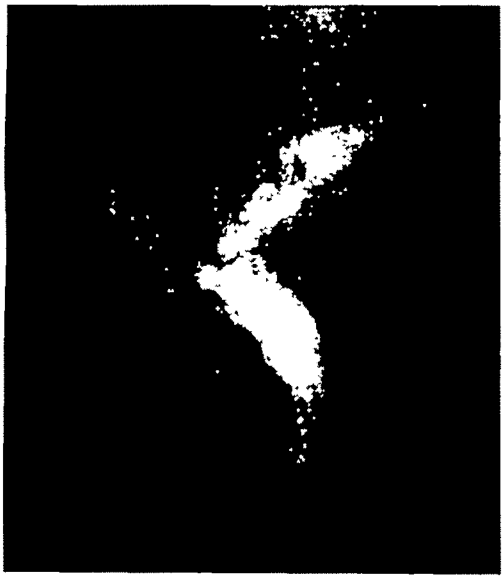

Fig. 1 Endoscopic retrograde cholangiogram showing stones in the common bile duct and bilateral intrahepatic ducts, dilated left duct system and tight stricture at the origin of the left hepatic duct

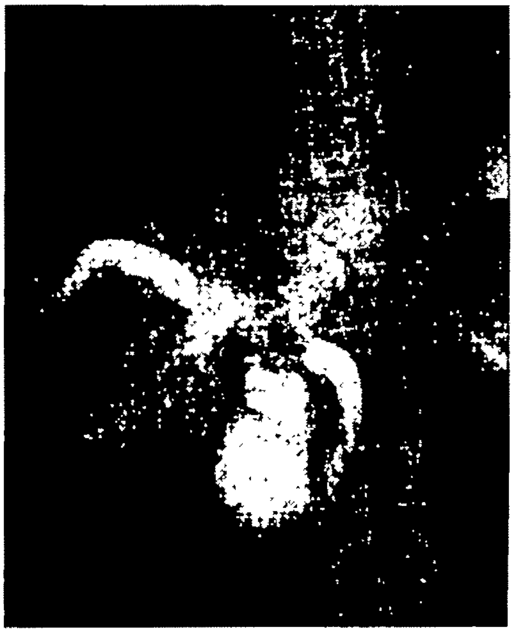

Fig. 2 Endoscopic retrograde cholangiogram demonstrating tight strictures at the origin of the left and right hepatic ducts, and dilated left duct system packed with stones proximal to the tight stricture

Discussion

Intrahepatic biliary stones have been shown to be difficult to eradicate, the only surgical procedure that has been shown to offer lasting cure for intrahepatic stones being hepatic resection. This is indicated when prolonged obstruction leads to destruction of the liver parenchyma. It can be performed with a low mortality rate in properly selected patients when the stones are located proximal to a strictured left segmental duct. Patients with atrophy and fibrosis of the lobe, abscess formation or cholangitic appearance in the surrounding liver parenchyma, and recurrent or retained stones that can not be removed by other methods, are suitable for hepatic resection[2,7–10]. Most previous authors considered that those who had diffuse or bilateral intrahepatic stones were excluded from hepatic resection because resection could be performed only on a hepatic segment or in a hepatic lobe. In these patients, it was expected that residual stones would remain in the unresected intrahepatic ducts[7,8]. However, if the liver parenchyma is largely destroyed, commonly the left liver, hepatic resection is indicated because the damaged liver would lead to cholangitis or recurrent stone formation. If the intrahepatic bile ducts are packed with stones but the liver is normal morphologically, the liver parenchyma should be preserved as the impacted stones can be eradicated by postoperative choledochoscopy supplemented by lithotripsy[5,6,15,16], to prevent the disease from involving the entire liver. In this study, 59 (15·1 per cent) of 392 patients with bilateral intrahepatic stones underwent hepatic resection.

Although hepatic resection for intrahepatic stones rarely leads to death, this procedure is not without risk.

The most frequent complications were wound infection, haemobilia and bile leakage, and most patients had infected bile. To prevent biliary fistula and haemobilia, a careful search for and meticulous closure of the bile duct opening, or even approximation of the edges of the transected liver surface, is advisable. The results of the present study are compatible with recent studies comparing patients who had hepatic resection[7,8] with those who did not (*Table 2*).

This study also highlights the problem of the concomitant occurrence of intrahepatic stones with cholangiocarcinoma. It has been reported that 5·0–8·7 per cent of patients with intrahepatic stones have concomitant cholangiocarcinoma[12]. Chronic proliferative cholangitis in the presence of intrahepatic stones could induce progressive changes leading to atypical epithelial hyperplasia, which might progress to cholangiocarcinoma[18]. Although it is not necessary to perform hepatic resection for all intrahepatic stones to prevent the development of concomitant cholangiocarcinoma, liver resection may reduce the risk of cholangiocarcinoma[19,20].

The incidence of complete stone clearance after operation for hepatolithiasis has been reported to range from 22 to 89·8 per cent[1–10]. However, results have been greatly improved by the development of the flexible choledochoscopy, ductal dilatation and stenting techniques, and stone fragmentation instruments. Recently, various operative procedures (bile duct exploration, hepatectomy, hepaticojejunostomy) combined with choledochoscopy and electrohydraulic lithotripsy have produced complete stone clearance in 89·8 per cent of patients[6]. The present series showed complete stone clearance rates for patients with bilateral intrahepatic stones who had undergone hepatic resection immediately after operation and at 1 year of 40 and 84 per cent respectively, rates that were significantly higher than those in the no-hepatectomy group. These findings are similar to those of other recent reports from Hong Kong[5–7], Japan[9,10] and Taiwan[8]. Failure to eradicate all stones in the group of patients without hepatectomy may be due to the high incidence of intrahepatic strictures with or without ductal angulation[1–10].

Although residual stones could be removed by postoperative choledochoscopy, this procedure is uncomfortable for patients. Postoperative choledochoscopy also causes cholangitis and abdominal pain[17]. This study shows that patients having hepatic resection for intrahepatic stones needed fewer postoperative choledochoscopic sessions, and that the procedure is associated with fewer recurrent stones than in patients not having hepatectomy, as reported previously[2,7–10].

Because of the low operative risk, fewer residual stones and low incidence of recurrent stones, hepatic resection is a satisfactory procedure for patients with bilateral intrahepatic stones when the destroyed liver parenchyma can be removed completely.

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Surgical workshop

Use of a biliary stent in laparoscopic choledochotomy for removal of duct stones

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Laparoscopic transcystic common bile duct (CBD) exploration is limited by the diameter of the cystic duct lumen, its direction and position of insertion into the CBD as well as by the size of the duct stones[1–5]. In cases where endoscopic retrograde cholangiopancreaticography (ERCP), sphincterotomy and transcystic removal of duct stones are not possible, laparoscopic CBD exploration similar to an open procedure is an attractive option in selected cases. Usually the operation follows the pattern of open surgery, with T tube placement. Use of a biliary stent to facilitate closure of the choledochotomy is now proposed. It also allows early discharge of the patient (free from drainage tubing). The stent can be removed later on an outpatient basis.

Surgical technique

The operating ports are inserted as in *Fig 1*. The cystic duct is identified, secured with titanium clips and left uncut to maintain traction on the CBD. The CBD is cleared carefully and identified by endoscopic needle aspiration. A stay suture is applied at the apex of the proposed choledochotomy to provide a tenting effect and to stabilize the CBD. A longitudinal choledochotomy adequate for the size of the ductal stones is made with microscissors. Duct stones are removed by endograspers or by milking the CBD with an instrument behind the hepatoduodenal ligament in the foramen of Winslow. The CBD is flushed with a Jacques catheter. A Dormia basket and balloon extractor (Escort II double-lumen balloon extractor, Duette; Wilson-Cook Medical, Winston-Salem, USA) are also used. Flexible choledochoscopy is usually performed but was not used in two instances in this series: in the first patient and when the instrument was being repaired. T tube cholangiography was also used to confirm and document complete stone clearance in one case when five stones were retrieved although preoperative ERCP indicated the presence of only three calculi.

A biliary stent (7–10-Fr Cotton–Leung biliary stent, 9 cm; Wilson Cook) is inserted into the choledochotomy and the distal end of the stent is threaded through the ampulla of Vater[4]. It is better to use the 10-Fr stent to avoid stent migration. Before suturing the choledochotomy, placement is checked by duodenoscopy, to ensure that the stent is protruding through the papilla and that it does not protrude too far into the duodenum. This can cause technical difficulty in removal at a later date, as happened in one patient.

Results

During the study period, 63 patients had CBD stones. Most were retrieved successfully by ERCP with sphincterotomy and seven patients underwent laparoscopic choledochotomy for removal of CBD stones (*Table 1*). Mean operating time was 2·9 (range 2–4) h. Feeding was started 1 day after operation. Five patients were discharged by the fourth postoperative day and two stayed for 10 and 12 days for family and social reasons. All patients had the biliary stent removed between 4 and 6 weeks after operation, without cholangiography. There were no bile leaks, retained stones or deaths. No patient developed symptoms of pancreatitis; serum amylase levels were not measured. One patient developed a chest infection which resolved with antibiotic treatment and chest physiotherapy.

Discussion

Laparoscopic CBD exploration may be considered for patients in whom ERCP sphincterotomy and stone extraction are not possible. After this procedure a biliary stent is used rather than a T tube because closure of the choledochotomy is technically easier as suturing is not encumbered by the vertical limb of the T tube. The biliary

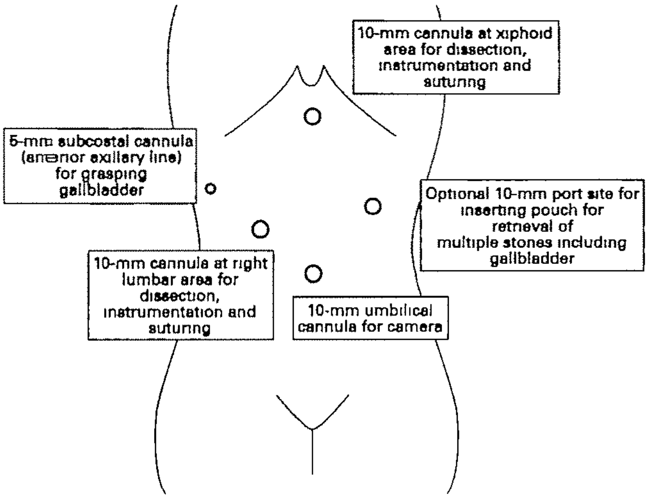
10-mm cannula at xiphoid area for dissection, instrumentation and suturing
5-mm subcostal cannula (anterior axillary line) for grasping gallbladder
Optional 10-mm port site for inserting pouch for retrieval of multiple stones including gallbladder
10-mm cannula at right lumbar area for dissection, instrumentation and suturing
10-mm umbilical cannula for camera

Fig. 1 Operative layout and position of instruments

Table 1 Clinical data on seven patients who underwent laparoscopic exploration of the common bile duct

No. of patients	7
Sex ratio (M:F)	2:5
Mean (range) age (years)	61 (46–89)
No. of stones removed	
1	3
2	1
>3	3
Size of stones (cm)	
>1·5	1
>2·0	2
>2·5	4
T tube cholangiogram to confirm clearance of stones*	1
Choledochoscopy to confirm clearance of stones*	5

*Removed and replaced by biliary stent after imaging in one patient with five stones

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stent is used for decompression and for facilitating bile drainage into the duodenum; a T tube is normally placed for the same reasons in open surgery. Patients can also be discharged earlier compared with those with a T tube as the stent can be removed later. Although it has not been the authors' practice, it is entirely feasible at the time of stent removal to inject contrast medium into the stent to outline the biliary system and detect any retained stones.

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Population-based study of cancer risk and relative survival following sphincterotomy for stones in the common bile duct

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Background Endoscopic sphincterotomy was introduced in 1974 as a procedure for removing stones in the common bile duct. To assess the long-term risk of cancer and relative survival, all patients who underwent this procedure at six different hospitals between 1977 and 1985 were identified.

Methods A total of 992 patients was identified and they were followed by linkage to the Swedish Death Registry and the Swedish Cancer Registry.

Results At 1 year or more after sphincterotomy there was no increased risk of cancer in the liver, gallbladder, bile duct or pancreas (standardized incidence ratio 0·80, 95 per cent confidence interval 0·3–1·9). Relative survival was lowered slightly in the first year after sphincterotomy, but did not differ from that of the background population thereafter.

Conclusion Endoscopic sphincterotomy for stones in the common bile duct does not appear to affect the risk of cancer in the pancreas, liver or bile ducts, nor does it affect long-term survival.

Endoscopic sphincterotomy of the sphincter of Oddi has been used as an effective method for removing stones from the common bile duct (CBD) since the introduction of the method in 1974 by Classen and Demling[1] and Kawai *et al.*[2]. At first, the procedure was confined to older patients because of concern for side-effects, such as pancreatitis, cholangitis and the potential risk for development of malignant tumours in the pancreas, bile ducts, gallbladder and liver[3]. However, during the 1980s, owing to the low frequency of short-term complications, an increased number of younger patients were subjected to sphincterotomy. This trend was further enhanced in the 1990s with the introduction of laparoscopic cholecystectomy. Although some authors recommend conversion to laparotomy when stones are found in the CBD[4], others advocate their removal by means of endoscopic sphincterotomy after surgery[3,5]. However, little is known about the long-term effects after sphincterotomy, even though there have been some descriptive studies showing infrequent benign long-term effects[6–11], such as cholangitis, pancreatitis, recurrent stones and stenosis.

Thus, to analyse the long-term effects of endoscopic sphincterotomy, a population-based cohort study with regard to survival and the risk of cancer incidence in the organs adjacent to the sphincter was conducted. The study consisted of 992 patients operated on between 1977 and 1985, followed through linkage to the Swedish Cancer Registry and Death Registry, with a median follow-up of 9 and 10 years respectively.

Patients and methods

The cohort

Endoscopic retrograde cholangiopancreatography (ERCP) was introduced in Sweden in 1977. During the 1970s and early 1980s there were six hospitals in which the method was used in central Sweden (*Table 1*). All patients in whom sphincterotomy was deemed necessary in the surrounding hospitals and medical centres were therefore referred to one of these six centres up to the mid-1980s. This enabled the identification of a population-based cohort of all patients subjected to ERCP at these six hospitals between the years 1977 and 1985. The patients were identified through registers of endoscopic retrograde cholangiography kept at each hospital in a uniform manner. Every endoscopic record contains information on the underlying reasons, findings and type of therapy implemented. All records were examined to identify all patients who underwent endoscopic sphincterotomy for stones in the CBD without a diagnosis of cancer in the pancreas, bile ducts, gallbladder or liver. Patients subjected to sphincterotomy with a finding of a suspected malignant stenosis were excluded from the cohort. Between 1977 and 1985, 992 patients underwent endoscopic sphincterotomy for stones in the common duct. The distribution between the hospitals is shown in *Table 1*.

Table 1 Distribution of 992 patients at the six hospitals

	No. of patients
Uppsala	297
Karolinska (Stockholm)	140
South Hospital (Stockholm)	68
Eskilstuna	318
Ludvika	103
Torsby	66

There were 447 men (45·1 per cent). The mean age of the patients was 70·4 (range 20–95, median 72) years. There was no difference in age between men and women.

Follow-up

All patients were identified by their national registration numbers, unique for each person in Sweden[12], and record linkages were made between the Swedish Cancer Register and the Swedish Death Register, both considered to be almost complete[13–15]. Through the Cancer Register, the patients were followed until diagnosis of cancer in the liver, gallbladder, bile ducts or pancreas or until 31 December 1991, with a follow-up of at least 6 (median 9) years. The national incidence of the four cancers is shown in *Fig. 1*[16]. Through the Swedish Death Register the patients were followed until death or until 31 December 1992 (median 10 years)

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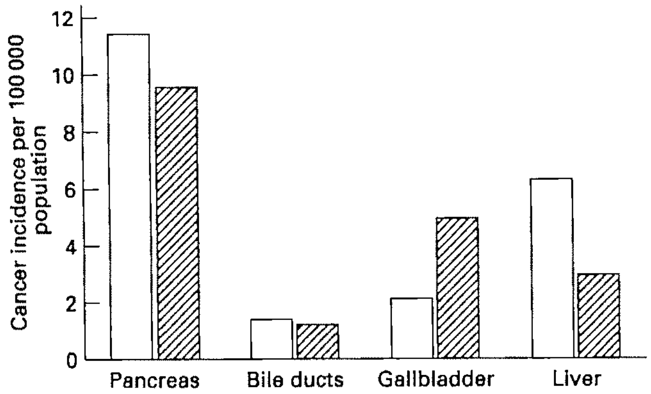

Fig. 1 Cancer incidence per 100 000 inhabitants in Sweden for cancer of the pancreas, bile ducts, gallbladder and liver. Rates are adjusted to the 1970 census. □, Men; ▨, women

Analysis

The expected number of cancers was calculated by multiplying the number of person-years for each sex by age-specific cancer incidence rates for 5-year age groups and calendar year of observation. These expected rates were derived from the total population of Sweden, but there should be no bias because the incidence of the cancers studied does not differ geographically in Sweden[16].

The standardized incidence ratio (SIR) was defined as the ratio of observed numbers of cancers to those expected. The 95 per cent confidence interval (c.i.) of the SIR was then calculated on the assumption that the observed number followed a Poisson distribution[17].

The standardized mortality ratio (SMR) was defined as the ratio of observed deaths in specific diagnostic groups to those in the background population. Relative survival was determined by means of life-table analysis, described by Hakulinen and Abeywickrama[18]

Results

Fifteen pancreatic cancers and 19 tumours of the gallbladder, bile ducts or liver were identified in the cohort. However, 13 of the pancreatic cancers and 16 of the cancers in the gallbladder, bile ducts or liver were diagnosed within 1 year after sphincterotomy and were excluded from subsequent analysis as they probably constituted microscopic cancers not yet detectable or missed at the time of sphincterotomy (*Table 2*). At 1 year or more after the sphincterotomy there were five cancers in the sites of interest, compared with the expected number of 6·27 (SIR 0·80, 95 per cent c.i. 0·3–1·9). Between 1 and 5 years there was one gallbladder cancer and one liver cancer 2 and 4 years after sphincterotomy respectively, compared with 3·23 expected of the four cancer types combined (SIR 0·62, 95 per cent c.i. 0·1–2·2). Five years or more after sphincterotomy there were two pancreatic cancers and one gallbladder cancer, compared with 3·04 expected (SIR 0·99, 95 per cent c.i. 0·2–2·9) (*Table 3*). An additional finding was one patient who was diagnosed with duodenal cancer 8 years after sphincterotomy.

After excluding all cancer cases diagnosed during the first year after sphincterotomy, relative survival was still decreased during the first year after sphincterotomy (0·97). However, 1 year or more after operation, the survival of patients who had sphincterotomy did not differ from that of the background population.

The high mortality during the first year after sphincterotomy appears to be related to the poor general condition of the patients: 84 patients (8·5 per cent) died during the first year, 23 within 30 days of sphincterotomy (30-day mortality rate 2·3 per cent). Eight deaths (0·8 per cent) were due to complications during or after sphincterotomy, such as perforation, septicaemia or bleeding. Furthermore, examination of the medical charts of patients who died within 1 year revealed that the underlying reason for ERCP as opposed to open surgery was that more than 50 per cent were considered unfit for open surgery. Analysis of the SMR during the first year after sphincterotomy showed significantly increased mortality from cardiovascular diseases, International Classification of Diseases (ICD)-7 400-468 and ICD-8 390-458 ($n = 35$, SMR 1·52, 95 per cent c.i. 1·06–2·11) and gastrointestinal diseases, ICD-7 530-588 and ICD-8 520-578 ($n = 27$, SMR 19·26, 95 per cent c.i. 12·7–28·0) compared with the general population.

Table 2 Incidence of cancer of the pancreas, gallbladder, liver and bile ducts after endoscopic sphincterotomy in the cohort

	Time after sphincterotomy (years)		
	<1	1–5	>5
No. of persons at risk	992	878	715
Cancer of the gallbladder, liver and bile ducts	16	2	1
Cancer of the pancreas	13	0	2

Table 3 Observed and expected numbers, and the standardized incidence ratio for cancer of the gallbladder, liver, bile ducts and pancreas

	Time after sphincterotomy (years)								
	1–5			>5			>1		
	Obs.	Exp.	SIR	Obs.	Exp.	SIR	Obs.	Exp.	SIR
Cancer of the gallbladder, liver or bile ducts	2	1·52	1·33 (0·2–4·8)	1	1·50	0·67 (0·0–3·7)	3	3·01	1·00 (0·2–2·9)
Pancreatic cancer	0	1·72	0	2	1·55	1·29 (0·2–4·7)	2	3·27	0·61 (0·1–2 2)
All four cancers	2	3·23	0·62 (0·1–2·2)	3	3·04	0·99 (0·2–2 9)	5	6·27	0·80 (0·3–1·9)

Values in parentheses are 95 per cent confidence intervals. Obs., observed; Exp., expected, SIR, standardized incidence ratio

Discussion

The main result of the present study is reassuring as no increased risk of cancer in the liver, bile ducts, gallbladder or pancreas was detected 1 year or more after endoscopic sphincterotomy. Furthermore, although the relative survival was decreased during the first year after sphincterotomy, survival after the first year did not differ from that of the background population. The increased mortality rate during the first year was confined to the first 30 days after the procedure, and was probably due to a combination of direct complications with the procedure as well as selection of patients in very poor condition, illustrated through findings in the medical charts and through the analysis of increased SMR in cardiovascular diseases.

The major strengths of this study are twofold: the inclusion of all cases within a defined population and time period, and the long follow-up of at least 6 years for cancer and 7 years for survival (median follow-up 9 and 10 years respectively).

There are, however, limitations: the small number of expected cancer cases, as an effect of the low incidence of the four types of cancer in the population, makes a cohort of even 1000 patients too small to rule out an excess risk lower than 2. However, the results of the present study indicate that patients who undergo sphincterotomy do not differ from the background population with respect to the incidence of cancer in sites adjacent to the sphincter, although an increased cancer risk 15 years or more after sphincterotomy cannot, of course, be ruled out.

An increased risk of cancer of the pancreas, bile ducts, gallbladder and liver is biologically plausible, as destruction of the sphincter of Oddi could lead to regurgitation of duodenal contents into the pancreatic and bile ducts followed by recurrent cholangitis or pancreatitis[8,10]. In the case of the pancreas this process could be further aggravated by regurgitation of bile into the pancreatic duct, which also has been discussed as a risk factor for pancreatic cancer[19]. The results of the present study, however, do not give any credence to such a mechanism as an important aetiological factor, at least not during the first 15 years after the procedure.

As there are no other studies of cancer occurrence after sphincterotomy, a comparison with previous studies is impossible. However, previous follow-up studies for benign disorders are in accordance with these results[11], showing late complications in the form of cholecystitis, cholangitis and restenosis in 21 (9·3 per cent) of 226 patients, compared with only five patients (0·2 per cent) without a gallbladder *in situ*. A previous Swedish study[7] of 43 patients who underwent transduodenal sphincterotomy with 20–25 years' follow-up showed no negative side-effects. The results of the present study are also in accordance with those of one other follow-up study of patients who had cholecystectomy[20]. Patients who had cholecystectomy combined with surgery of the CBD, which in many patients would have led to destruction of the sphincter of Oddi or to a choledochoduodenal fistula, were analysed separately. There was no increased risk for cancer of the bile ducts (SIR 0·27, 95 per cent c.i. 0·06–0·80) or liver (SIR 0·98, 95 per cent c.i. 0·66–1·40) 10 years or more after operation.

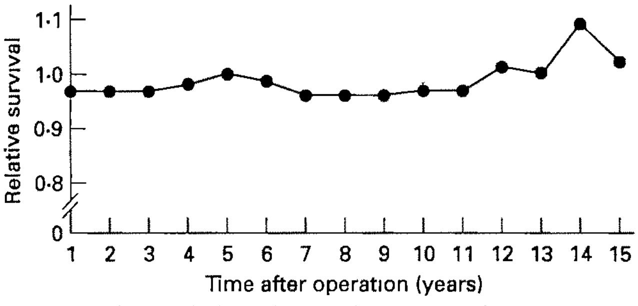

Fig. 2 Relative survival 1–15 years after endoscopic sphincterotomy

Cancer of the gallbladder in the present study constituted a special problem as sphincterotomy for many patients was either preceded or followed by cholecystectomy. In a previous Swedish study[21] of 276 patients subjected to endoscopic sphincterotomy because of stones in the CBD, 46 per cent of patients were without a gallbladder at the time of the procedure, which is a substantially higher proportion than in the background population. A comparison of the incidence of cancer of the gallbladder in the present cohort to that of the background population is even harder to perform owing to the fact that gallstones are the only established risk factor for cancer of the gallbladder[22]. As most stones in the bile duct emanate from the gallbladder, this means that the present cohort had fewer gallbladders at risk but were almost all exposed to the only accepted risk factor for this malignancy. The occurrence of just one case of gallbladder cancer in the cohort during follow-up is therefore difficult to interpret, but a strong association between sphincterotomy and gallbladder cancer seems inconceivable.

The hypothesis did not include duodenal cancer as a site of interest. Tumours are very rare in the duodenum compared with the other four sites (incidence is 0·45 per 100 000 population) and the finding of one case of duodenal cancer in the cohort should therefore be interpreted with caution[16]. However, even if duodenal cancer were to be included as a site of interest, the SIR for the five sites would still be less than 1, 1 year or more after sphincterotomy.

In summary, no serious long-term side-effects were found following sphincterotomy for stones in the CBD. The strategy of endoscopic sphincterotomy following laparoscopic cholecystectomy introduced in the late 1980s does not seem to have any long-term adverse side-effects, but further studies with even longer follow-up are needed.

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Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis

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Background Many patients with severe acute pancreatitis develop organ system failure during the first few days of illness, and this accounts for the majority of early deaths. No specific therapy is available and treatment remains supportive.

Methods In a randomized controlled trial conducted in 11 hospitals in the West of Scotland, 50 patients with predicted severe acute pancreatitis were selected from 188 screened over a 14-month period. Patients received placebo or lexipafant, a potent platelet-activating factor antagonist, by continuous intravenous infusion at a dose of 100 mg/day for up to 7 days. Early systemic complications were assessed by the measurement of organ failure scores.

Results There was a significantly greater fall in organ failure score in the treatment group during the 7 days of study (mean and median changes in organ failure score were 0·17 and 0 in the placebo group *versus* − 1·42 and − 1 in the treatment group; $P = 0{\cdot}003$, Wilcoxon rank sum test), associated with trends towards a reduction in mortality and a reduced incidence of systemic complications.

Conclusion These results suggest that lexipafant may be a useful adjunct to full supportive care in the early management of patients with severe acute pancreatitis.

In patients with severe acute pancreatitis, two separate types of complication are recognized[1]. During the first week, patients have a systemic illness characterized by varying degrees of organ failure. Local pancreatic complications predominate in the second and third weeks, although these may also lead to organ failure as a consequence of sepsis. The management of pancreatic complications in the later phase of illness lies in the hands of the surgeon and the interventional radiologist, but there remains no specific treatment for patients developing early organ failure in acute pancreatitis, and management remains supportive.

Previous attempts at early treatment of acute pancreatitis have been directed at reduction of pancreatic secretion[2,3], protease inhibition[4–6], peritoneal lavage[7] and enhancement of reticuloendothelial activity[8]. Despite encouraging results in experimental pancreatitis, these approaches have met with almost universal failure when examined in controlled clinical trials.

Recent advances in our understanding of the pathophysiology of the early systemic illness in patients with acute pancreatitis have cast doubt on the rationale behind these clinical trials and have led to the development of a new therapeutic approach in acute pancreatitis. There is evidence from experimental[9–12] and clinical[13–16] studies that the systemic complications of acute pancreatitis are associated with increased proinflammatory cytokine secretion and subsequent neutrophil activation. One of these cytokines, platelet-activating factor (PAF), has been the subject of recent interest. PAF is a lipid mediator produced from cell membrane phospholipid by the enzymatic action of phospholipase A_2 and is known to be released by activated monocytes–macrophages, neutrophils, platelets and endothelial cells[17]. It has been shown to induce platelet aggregation and activation, neutrophil and monocyte activation and to increase vascular permeability[17], and has been implicated in the pathophysiology of experimental pancreatitis[18,19].

Lexipafant is a potent inhibitor of PAF; it binds to the PAF receptor with an avidity that is seven times greater than that of PAF itself. In a previous study reported by Kingsnorth and colleagues[20] in Liverpool, lexipafant at a dose of 60 mg/day for 3 days was reported to reduce the incidence of organ failure in an unselected group of patients with acute pancreatitis, where only 29 met the criteria for severe acute pancreatitis. However, many patients with mild pancreatitis will recover without intervention and any new treatment should be focused on patients with severe attacks of pancreatitis. The aim of the present study, therefore, was to examine the therapeutic potential of lexipafant in the prevention and treatment of organ failure in patients with severe attacks of acute pancreatitis.

Patients and methods

Patients

Between April 1994 and May 1995, 188 patients with acute pancreatitis admitted to 11 National Health Service (NHS) hospital trusts in the West of Scotland were referred for study assessment. Patients were recruited if, at the time of assessment, they had a clinical picture consistent with acute pancreatitis and satisfied the following criteria: (1) assessed within 72 h of the onset of pain; (2) serum amylase concentration more than four times the upper limit of the normal range; (3) written informed consent provided; and (4) predicted severe acute pancreatitis. For the purposes of this study, predicted severe acute pancreatitis was defined as one or more of the following criteria: (a) an Acute Physiology And Chronic Health Evaluation (APACHE) II score greater than 5 on admission; (b) three or more positive Glasgow prognostic criteria; and (c) a C-reactive protein level of 120 mg/l or more.

An APACHE II cut-off score of 6 or more was chosen as this level would be expected to include almost all patients who subsequently developed systemic complications while excluding

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half of the patients with mild self-limiting attacks[21]. Previous experience suggested that this would result in a study population with an overall incidence of organ failure of 40 per cent and a mortality rate of 20 per cent. Exclusion criteria were pregnancy, endoscopic retrograde cholangiopancreatography-induced pancreatitis, concomitant oral anticoagulant therapy, other trial drugs within 3 months before study entry, and previous use of lexipafant. All patients were assessed by a single investigator (F.C.) for eligibility.

A total of 51 patients were recruited: 27 received treatment (lexipafant) and 24 received placebo (aqueous buffer). One patient in the lexipafant group was later excluded from analysis as her hyperamylasaemia and abdominal pain were due to a dissecting aortic aneurysm. The groups were matched for age, sex distributiobn and APACHE II score at study admission (*Table 1*).

Gallstones and alcohol were the most common aetiologies, accounting for almost 80 per cent of cases. In the placebo group two patients had other identifiable causes. One patient was thought to have had steroid-induced pancreatitis and a second, with recurrent acute pancreatitis, had pancreas divisum.

Study design

The trial was conducted as a randomized prospective study comparing lexipafant with placebo. Investigators and patients were unaware of the nature of the trial infusion.

Recruitment and randomization

On admission of a patient with acute pancreatitis, medical staff at participating hospitals contacted the study coordinator (F.C.) who assessed patient eligibility. If the entry criteria were met, patients were allocated a treatment pack containing either lexipafant or placebo. Packs were numbered sequentially and prepared in advance by British Biotech (Oxford, UK). A copy of the randomization codes was provided with the clinical supplies. These were in sealed envelopes which were collected at the end of the study.

Treatment

Treatment packs contained either lexipafant 100 mg or placebo in a volume of 20 ml which was added to 0·9 per cent saline to give a final volume of 500 ml. The placebo was buffered saline solution. Patients received an initial intravenous loading bolus dose of 20 ml (4 mg) followed by a continuous intravenous infusion of 20 ml/h. Treatment was continued for 5 days in patients with an admission APACHE II score of 6–8 ($n = 7$) and for 7 days if the admission APACHE II score was greater than 8 ($n = 43$). In both groups of patients, trial infusion was discontinued earlier if there was full clinical resolution.

Table 1 Characteristics of patients in the two study groups

	Placebo	Treatment
No. of patients	24	26
Sex ratio (M:F)	14.10	15:11
Median (range) age (years)	65·5 (38–88)	64 (35–88)
Median (range) APACHE II score	10 (6–20)	12 (6–24)
Gallstones	12	12
Alcohol	6	9
Idiopathic	4	5

APACHE, Acute Physiology And Chronic Health Evaluation

All routine clinical management remained at the discretion of the senior medical staff in participating hospitals. No patient received prophylactic antibiotic therapy.

Study endpoints

The study was scheduled to run for 12 months, over which period it was expected that 50 patients would be recruited. The primary endpoint of this study was a difference in organ failure scores. A sample size of 25 patients per group would enable a difference to be demonstrated between the two groups of a change in mean organ failure score of 2 (equivalent to reversal of organ failure in one system) with $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}20$[22].

As secondary endpoints, the incidence of development of new organ failure was assessed, as was the incidence of reversal of pre-existing organ failure after completion of the trial infusion.

Assessment of clinical course

The study coordinator (F.C.) or research nurse reviewed each patient daily for 8 days and calculated APACHE II scores for the previous 24 h. Venous blood was taken for daily haematology and biochemistry estimations. Using information collated from the daily review and laboratory investigations, the organ failure score (*Table 2*) was calculated for each patient for each day of the study. Many organ failure scoring systems are available and the system selected for the present study[23] was chosen as its definitions of organ failure are similar to those for acute pancreatitis adopted following the Atlanta symposium[1]. An organ failure score of 2 or more for any organ equated to the accepted definitions of clinically significant organ failure. The only modification of this for the present study was the exclusion of the hepatic score (measured by serum bilirubin) as many patients with acute pancreatitis develop varying degrees of hyperbilirubinaemia secondary to cholestasis, rather than to true hepatic dysfunction.

During the study period each patient underwent abdominal ultrasonography or, as clinically indicated, contrast-enhanced dynamic computed tomography. Patients were followed for 28 days from the start of treatment and any adverse events or complications occurring since the last review were noted.

Statistical analysis

The difference between admission organ failure and organ failure 7 days after commencement of trial infusion for the two treatment groups was compared with the Wilcoxon rank sum test, as the sample variances differed significantly between groups and because the data were not distributed normally. An interaction test was carried out using a general linear model to examine the effect of treatment on the subgroups of patients

Table 2 Organ failure scoring system[23]

	Score				
System	0	1	2	3	4
Cardiovascular (systolic blood pressure, mmHg)	> 90	< 90 (fluid responsive)	< 90 (not fluid responsive)	< 90 (pH < 7·3)	< 90 (pH < 7·2)
Pulmonary (P_{aO_2}/F_{iO_2})	> 400	400–301	300–201	200–101	≤ 100
Central nervous system (Glasgow)	15	14–13	12–10	9–6	≤ 5
Coagulation (platelets) (× 10⁹/l)	> 120	120–81	80–51	50–21	≤ 20
Renal (creatinine, μmol/l)	> 134	134–169	170–310	311–439	≥ 440

P_{aO_2}, arterial partial pressure of oxygen; F_{iO_2}, fraction of inspired oxygen with and without pre-existing organ failure. The effect of treatment on mortality and the incidence of organ failure and organ failure resolution were examined with the χ^2 test or Fisher's exact test where appropriate

Ethics

The study protocol was given ethics committee approval from the 11 NHS hospital trusts involved.

Results

Overall incidence of complications and mortality

The overall mortality rate was 18 per cent (nine of 50), confirming the relative severity of acute pancreatitis in the patients recruited to the study. Six of the 24 patients in the placebo group died, and three of 26 in the treatment group ($P = 0{\cdot}36$, Fisher's exact test). The overall incidence of organ failure within the first week of admission was 62 per cent (31 of 50), and the incidence was similar in the two groups of patients (17 of 26 in the treatment group *versus* 14 of 24 in the placebo group). The majority (77 per cent) of these patients had organ failure before starting the trial infusion.

Three patients in the placebo group died from multiple organ failure associated with severe pancreatitis within the first week of illness. In the treatment group the only early death occurred in a patient with severe chronic obstructive pulmonary disease who developed respiratory failure but was not considered suitable for artificial ventilation. Three patients, two in the placebo group and one in the treatment group, died from sepsis resulting from infected pancreatic necrosis between weeks 4 and 7 after admission. Two patients, one in each group, died after having made an apparent recovery from the presenting attack of pancreatitis. One died from sepsis following cholecystectomy, at which a pancreatic carcinoma was discovered, and the other died from cardiorespiratory arrest during a subsequent admission although a definite cause of death was not determined.

Effect of lexipafant on organ failure score

The organ failure score was calculated every day for the first 7 days of illness, or until death if this occurred earlier. The mean organ failure score was then calculated for each group at entry to the study and daily for up to 7 days. Subjects who died before 7 days had their scores carried forward to the day 7 timepoint. The mean(s.e.m.) and median organ failure scores in the placebo group were 1·6(0·3) and 1 respectively at study entry, and 1·8(0·6) and 0 at 7 days (*Fig. 1*). In the treatment group the mean(s.e.m.) organ failure score was 2·1(0·2) (median 2) at entry and 0·7(0·2) (median 0) at 7 days. The mean and median differences in organ failure score at 7 days in the placebo group were 0·17 and 0 *versus* −1·42 and −1 in the treatment group ($P = 0{\cdot}003$, Wilcoxon rank sum test) (*Fig. 1*).

There was a significant effect of lexipafant on the change in organ failure scores whether or not organ failure was present at entry into the study ($P = 0{\cdot}003$, interaction test).

None of the patients in the treatment group had a deterioration in organ failure score after 7 days of treatment, compared with seven in the placebo group

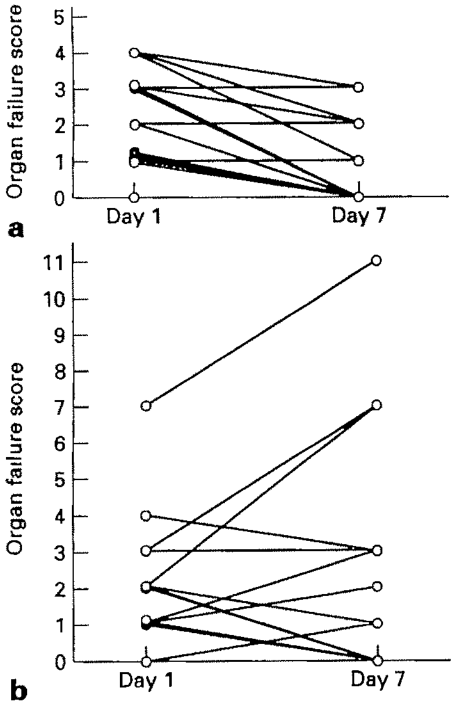

Fig. 1 Changes in the organ failure score in patients receiving a lexipafant and b placebo

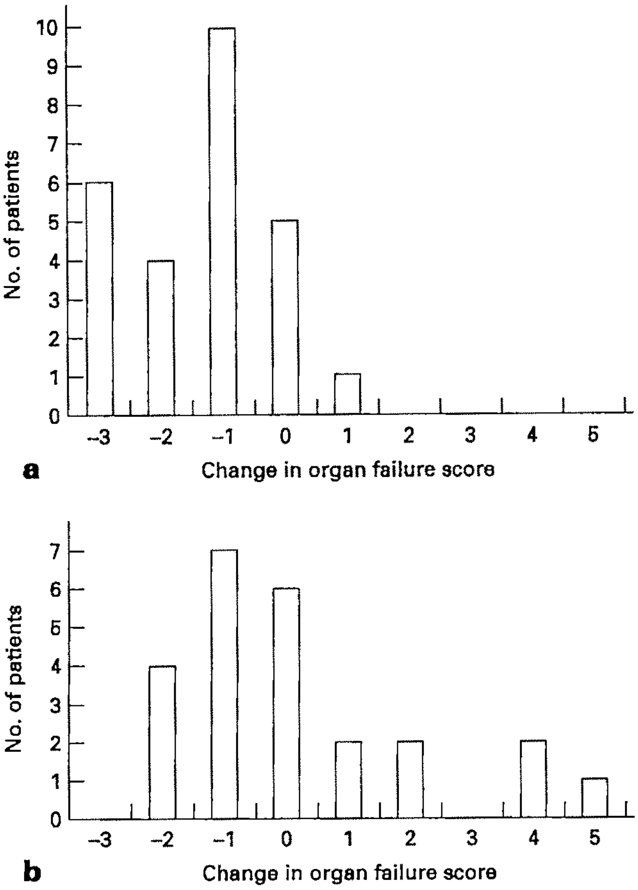

Fig. 2 Number of patients with each change in organ failure score when receiving a lexipafant and b placebo

($P = 0{\cdot}01$, Fisher's exact test) (*Fig. 2*). Six patients on placebo and five on lexipafant had an unchanged organ failure score at day 7.

Incidence of organ failure

Of the 50 patients entering the study, 26 had no organ failure (organ failure score of less than 2) on admission, 11 in the treatment group and 15 in the placebo group. There was no significant difference in the number of patients from this subgroup who developed failure in at least one organ system during the first week after admission. Five of the 15 patients in the placebo group developed new organ failure during this time, of whom four had persisting organ failure at day 7. In the treatment group, two of the 11 patients developed transient organ failure during the first few days but neither had persisting organ failure at day 7 ($P = 0{\cdot}18$, Fisher's exact test).

Effect of lexipafant on resolution of organ failure

Fifteen patients in the treatment group and nine in the placebo group had organ failure (organ failure score of 2 or more) on admission to the study. There was no significant difference between groups in the proportion of patients with complete resolution of organ failure after 7 days of treatment. Nine of the 15 patients in the treatment group had complete resolution of organ failure at 7 days compared with five of nine in the placebo group ($P > 0{\cdot}2$, χ^2 test).

Hospital stay

The mean length of hospital stay was similar for patients in the treatment and placebo groups, being 13·3 and 14·9 (median 9·0 and 10·5) days respectively.

Discussion

In this study a significantly greater reduction in organ failure score was found with lexipafant treatment compared with placebo. This was in part due to the increasing organ failure scores in seven patients in the placebo group, a finding that was absent in the treatment group. In addition, examination of the effect of lexipafant on patients with and without pre-existing organ failure showed a significant effect of treatment in both groups of patients. These findings suggest that lexipafant may be of value in both the prevention and treatment of early organ failure in acute pancreatitis.

In the assessment of outcome from acute pancreatitis and the therapeutic effect of a trial drug, it has been common practice to assess mortality and the incidence of local and systemic complications. There are two problems with this approach. First, to ensure sufficient statistical power, any such study would be required to recruit at least 150 patients with predicted severe pancreatitis in each limb simply to assess the effect on morbidity[22]. Many more patients would be required before the effect of the drug on mortality could be assessed and a study of this magnitude has not yet been published in acute pancreatitis. Second, when assessing the effect of a drug on early systemic complications, it is difficult to categorize patients who have evidence of organ failure on admission to hospital. For these reasons, the primary endpoint for this study was the effect of the trial drug on the organ failure score of the treatment group. It was reasoned that this would provide a more sensitive assessment of therapeutic potential and, if encouraging, would be justification for allocation of the resources necessary for a large multicentre trial

The study was of insufficient size to assess the effect of lexipafant on the incidence of organ failure, organ failure reversal or mortality, but trends in favour of the treatment group were seen in all of these indices and the results are therefore compatible with the treatment effect suggested by the reduction in organ failure scores.

The results of the present study are similar to those reported by Kingsnorth and colleagues[20], in which 29 patients had predicted severe pancreatitis with a mortality rate of 14 per cent and there were no deaths in the remaining 54 patients with predicted mild pancreatitis. Although the Liverpool study recruited a greater number of patients, the present study selected patients on the basis of a raised APACHE II score on admission, and this was reflected in the higher proportion of patients with organ failure in the present study (62 *versus* 30 per cent) and the higher overall mortality rate (18 *versus* 5 per cent). It should be noted that the 50 patients in the present study were recruited from a total of 188 screened over the 13-month period of study.

PAF has been implicated in the pathophysiology of experimental pancreatitis, but its role in acute pancreatitis in humans is unclear. This group has previously shown that mononuclear phagocyte activation occurs in acute pancreatitis, associated with increased secretion of the proinflammatory cytokines tumour necrosis factor (TNF) α, interleukin (IL) 6 and IL-8[15]. Serum levels of IL-6[24–26] and IL-8[27] are also increased in patients with severe pancreatitis. PAF is a lipid mediator which is also secreted by mononuclear phagocytes as well as other cell types, including granulocytes and platelets, and has potent effects on neutrophil activation, platelet aggregation and endothelial cell function[17]. PAF has been shown to induce the release of TNF-α from monocytes[28] and the effect of PAF on neutrophil superoxide radical production is greatly enhanced by preincubation with TNF-α[17]. PAF antagonists have been reported to ameliorate the toxic effects of TNF-α in an experimental model[29] and favourably to affect the outcome from experimental acute pancreatitis when given some time after the insult[30].

PAF antagonists may therefore influence the outcome from acute pancreatitis in a number of ways. Local pancreatic inflammation may be reduced, secretion of proinflammatory cytokines by mononuclear phagocytes may be inhibited, the effects of such cytokines on granulocytes and other cells may be diminished, and the degree of granulocyte activation may be lessened. The relative importance of the effect of PAF antagonism on these inter-related components of the inflammatory response has yet to be determined.

Many factors in the care of patients with severe acute pancreatitis may influence outcome. Adequate early fluid resuscitation, the early detection and treatment of systemic complications, the aggressive management of coexisting cholangitis, and the recognition and timely treatment of septic pancreatic complications will all influence outcome. There is, however, a group of patients who develop deteriorating early organ failure for which, at present, no specific treatment is available. The present study provides evidence that lexipafant may minimize such systemic complications and may be useful as an adjunct to good supportive care.

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Short note

Laparoscopic treatment of biliary peritonitis after T tube removal in patients undergoing orthotopic liver transplantation

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The incidence of biliary peritonitis after T tube removal in patients undergoing orthotopic liver transplantation (OLT) is high[1]. This incidence has declined with the increasing use of end-to-end choledochocholedochotomy without a T tube as a biliary reconstruction technique[2]. However, the authors still use a T tube when the calibre of both bile ducts is small and there is a risk of anastomotic stricture.

Currently, the commonest treatment of biliary peritonitis after T tube removal is non-operative, with insertion of a percutaneous or nasobiliary drain[1]. Classical surgical treatment is reserved for cases in which these measures fail. Two patients with biliary peritonitis following T tube removal are described, who were treated via the laparoscopic approach as an alternative to laparotomy when conservative measures failed.

Patients and methods

A 49-year-old man underwent OLT for hepatitis B-positive postnecrotic cirrhosis, and a 47-year-old man underwent OLT for hepatitis C-positive postnecrotic cirrhosis associated with a 3-cm hepatocarcinoma injected with alcohol 3 months earlier. In both cases, a biliary anastomosis was performed using end-to-end choledochocholedochotomy with a T tube because of the small size of the two bile ducts. Triple immunosuppression therapy was used (cyclosporin, corticoids and azathioprine). Three months later the T tube was removed in both cases without difficulty The clinical course was similar in both patients: a sharp pain was reported immediately in the right hypochondrium, which later spread to the whole of the abdomen. Ultrasonography confirmed the presence of intraperitoneal fluid. Nasobiliary drainage was attempted, but this was technically impossible in both cases Nasogastric aspiration, intravenous fluid and antibiotics did not result in improvement, and the patients underwent surgery 24 and 36 h respectively after T tube removal, for biliary diffuse acute peritonitis.

A laparoscopic approach was attempted by inserting an umbilical trocar for the straight telescope using Hasson's open technique. There were no adhesions in the inframesocolic space. In both cases, however, there were loose adhesions in the right hypochondrium, from the omentum and hepatic flexure of colon to the liver, and a diffuse acute biliary peritonitis. Two 5-mm trocars were inserted, one in the left iliac fossa and the other in the right lateral quadrant for inserting the dissection forceps, scissors and coagulation hook. The amount of bile aspirated was 700 and 900 ml respectively. In both cases the adhesions were subsequently detached from the right hypochondrium, and this provided a perfect view of the fistulous orifice in the bile duct, where a Penrose drain was fitted; this was brought out through the right hypochondrium. The operating time was 95 and 90 min respectively. Neither required analgesics during the postoperative period. The amount of bile drained on the first day after operation was 350 and 500 ml respectively. This amount decreased, and both patients were discharged on the fourth day after operation.

Discussion

The classical treatment of biliary peritonitis after T tube removal following OLT is laparotomy, lavage of the cavity and drainage of the right hypochondrium[3-5]. Following these steps, the authors operated on four patients via a laparotomy, with a similar operating time (mean 108 min) but with greater analgesic requirements and a longer hospital stay (7 days)[3] than with the laparoscopic approach. However, in recent years the management of this pathology has changed because of the efficacy of conservative treatment, basically the use of a nasobiliary drain[1] inserted by the endoscopist and left until the fistulous orifice closes. This is currently the authors' preferred treatment option, although there are occasions when it is not possible to fit a nasobiliary drain because of technical difficulties, as occurred with these two patients, or because no endoscopist is available. Percutaneous drains have been used for bilomas[3], but in cases of biliary peritonitis this technique is not used because in the absence of a perihepatic bile collection there is a risk of injuring neighbouring viscera, and also because bile collects in the inframesocolic space. In these circumstances, once biliary peritonitis is established, surgical treatment is indicated.

Before laparotomy in these two patients, a laparoscopic approach was attempted using Hasson's technique. No adhesions were found in the inframesocolic space, probably because OLT surgery is limited to the right hypochondrium. Aspiration and lavage of the cavity was simple, and dissection of the subhepatic space was favoured by the loose nature of the adhesions, probably related to the use of corticoids. The postoperative course of both patients was comfortable, and they were discharged on day 4. In conclusion, patients with biliary peritonitis after OLT in whom conservative treatment fails may benefit from laparoscopic management.

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Importance of eliminating portal flow to produce large intrahepatic lesions with interstitial laser coagulation

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Background Interstitial laser coagulation is a local treatment modality for solid tumours, such as liver metastases. Perfusion by the vascular system can transfer heat from the treatment site, thereby reducing the volume of destroyed tissue.

Methods This effect was investigated in a pig model ($n = 10$). Lesions were produced in the liver with four interstitial laser fibres (5 W per fibre for 6 min): (1) with flow through the liver ($n = 9$); (2) with the portal vein clamped ($n = 8$); and (3) with both hepatic artery and portal vein clamped ($n = 6$). The pigs were killed and the liver was dissected; lesions were assessed macroscopically and microscopically.

Results The volume of the lesion was significantly larger when portal flow was eliminated (30·6 *versus* 6·4 cm^3, $P < 0·001$).

Conclusion Hepatic blood flow substantially reduces the size of the lesion produced by laser coagulation. Portal flow should therefore be occluded during laser treatment to produce lesions of clinically relevant dimensions.

Fifty per cent of patients with colorectal cancer eventually develop liver metastases. Mean survival in these patients is 9 months[1]. In a selected group, surgical resection improves the 5-year survival rate to 20–40 per cent[2]. Despite intensive research in various disciplines, no definitive treatment modality has been established for patients with irresectable metastases confined to the liver[3].

In 1983 the concept of interstitial laser coagulation was introduced as a new technique for local tissue destruction[4]. This method comprises the insertion of one or more light-delivery fibres directly into the tumour. The light is absorbed by the tissue and produces an immediate temperature rise, which above 60°C results in tissue coagulation. Several experimental studies[5,6] and small clinical series[7,8] have shown the feasibility of interstitial laser coagulation. Recently Tranberg *et al*[9] reported a series of 12 patients treated at laparotomy. Vogl *et al.*[10] treated 20 patients percutaneously and Bown and co-workers[8,11] have now treated more than 100 patients percutaneously (personal communication).

As each study defines its own criteria for selection and evaluation, the findings are difficult to compare. The overall conclusion, however, is that interstitial laser coagulation is effective in destroying tumours smaller than 2 cm in diameter. Larger tumours are variably and incompletely destroyed and recurrence occurs in these lesions. There may be several reasons for the lack of success in larger tumours. First, the size of a lesion created by a single conventional laser fibre is maximally 2 cm in diameter[12]. Second, various previous studies have shown preservation of viable cells surrounding larger vessels after interstitial laser coagulation. These cells probably survive as a result of the cooling effect provided by blood flow[5,13].

To overcome these obstacles, the authors have recently developed a laser fibre with a heat-resistant cylindrical diffusing tip[14]. These fibres produce larger lesions by emitting the laser light over the entire diffusing end. In addition, a beam-splitter was developed, dividing one laser beam into four equal beams to feed four implanted laser fibres simultaneously. With these new techniques, lesions of 5 cm in diameter can be produced in *ex vivo* liver[15].

The purpose of this study was to investigate this treatment, and the influence of hepatic blood flow *in vivo*. Size and configuration of the lesions were assessed after interstitial laser coagulation in a porcine model with and without clamping the large hepatic vessels.

Materials and methods

Laser equipment

A neodymium yttrium–aluminium–garnet (NdYAG) laser (wavelength 1064 nm, MBB 4060N; Dornier, Munchen, Germany) was connected to an optical beam-splitting device (Rare Earth Medical, West Yarmouth, Massachusetts, USA), supplying four fibres with cylindrical diffusing tips 2 cm in length (outer diameter 1·65 mm, Lightstic; Rare Earth Medical).

Animals and anaesthesia

Ten female pigs of pure Yorkshire breed (75–90 kg, age 8–12 months) received a standard diet; on the experimental day they were kept fasted. The animals were anaesthetized with azaperon 0·05 ml/kg intramuscularly and, after administering ketamine 10 mg/kg intramuscularly and thiopental 10 mg/kg intravenously, they were intubated and ventilated artificially with a mixture of nitrous oxide and oxygen (1:2) and 1·5 per cent isoflurane. During ventilation, anaesthesia was maintained with pancuronium 4 mg intravenously and fentanyl 0·1 mg intravenously. After the experimental procedures the pigs were killed without recovery from anaesthesia with a bolus intravenous injection of pentobarbital. The experimental

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protocol adhered to rules laid down in the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of Erasmus University.

Experimental procedures

Surgical procedures were performed in a fully equipped animal operating theatre, using standard sterile surgical techniques. For optimal exposure of the different liver lobes, a thoraco-laparotomy was performed. The liver was mobilized and the structures in the hepatoduodenal ligament were identified To ensure reproducible fibre insertion, a custom-built Perspex template with four openings at a mutual distance of 2 cm was used. After positioning this template on the liver, four intravenous cannulas (14-G Adsyte; Becton Dickinson, Madrid, Spain) were inserted and the needles were withdrawn. The laser fibres were put through the cannulas, which were then withdrawn entirely out of the liver. After laser application the liver capsule was marked with diathermy.

Experimental groups and laser treatment

Laser treatment was carried out with either physiological flow through the liver ($n = 9$, flow condition), with clamping of the portal vein ($n = 8$, partial flow condition) or with clamping of both portal vein and hepatic artery ($n = 6$, no-flow condition). The vessels were clamped just before insertion of the introduction cannulas. Flow was restored immediately after laser coagulation; flow occlusion never exceeded 15 min. Experiments in *ex vivo* liver[15] had shown an optimal synergistic effect between the four fibres when placed 2 cm apart and illuminated with 5 W for 6 min. This combination was also used in this study.

Lesion assessment

Immediately after the experiment, the animals were killed and the liver was removed. The coagulated lesions were sliced perpendicularly to the plane of fibre insertion. The presence of fusion of the coagulated zones surrounding the fibres was noted. The extent of the lesion was determined, using the macroscopically detectable whitish colour change of the coagulated liver tissue. Height (h, plane along fibre insertion) and width (w, largest plane perpendicular to fibre insertion) of the lesions were measured with callipers. The volume was then calculated with the formula $h \times w^2 \times \pi/6$. When separate coagulation zones surrounding the four fibres were present, the separate calculated volumes were summed to obtain the total coagulated volume.

Histology

Tissue was fixed in 3·6 per cent formaldehyde, dehydrated in graded ethanol solutions and xylene, and then embedded in paraffin. Sections 5 μm thick of the entire plane of dissection were cut for light microscopy and then stained with haematoxylin and eosin.

Statistical analysis

For each flow condition, mean volume and range were calculated across the number of lesions. Values are expressed as mean (range). Raw data were analysed with an unbalanced repeated-measures analysis of variance model with flow as an independent variable and volume as dependent, regarding the pig as the experimental unit. To test for differences in volume by flow condition, the Wald test was used. To test for the dependency of fusion (yes/no) on flow, an exact trend test was used in 2 × 3 contingency tables, stratified by experimental animal. $P < 0·05$ was considered statistically significant.

Results

Thirty-one lesions were produced, resulting in 23 evaluable lesions in nine pigs. One pig died before laser treatment, from anaesthetic complications. Five lesions were not included in the evaluation because of doubt on laser output, owing to technical malfunction. In three experiments inadequate withdrawal of the cannulas resulted in melting and massive carbonization. This problem was resolved by changing from black to transparent cannulas.

Macroscopy

A circular, well defined zone of coagulated tissue was found surrounding the insertion sites of the four fibres. Under the flow condition, four separate circular zones could be identified (*Fig. 1*). Under partial flow and no-flow conditions, however, fusion of the coagulated zones between the fibres always occurred. This coagulated zone under the partial and no-flow conditions was encircled by a haemorrhagic rim (*Fig. 1*). *Table 1* summarizes the results. The coagulated volume with flow (6·4 (1·1–12·6) cm^3) was significantly smaller than with partial flow (30·6 (24·6–48·6) cm^3) and with no flow (26·6 (19·5–34·5) cm^3) ($P < 0·001$). No significant difference was found between the coagulated volumes under the partial *versus* no-flow condition ($P = 0·54$). Significantly more fusion of the lesions was found under the partial and no-flow conditions than with the flow condition ($P = 0·005$).

Microscopy

In the area of coagulation, three zones could be distinguished. Directly adjacent to the fibre tracks, elongated spindle-shaped cells were visible, surrounded by a broad area containing dilated sinusoids and hepatocytes with vacuolated cytoplasm. The outer, macroscopically detectable, haemorrhagic zone consisted of hepatocytes with less vacuolated cytoplasm and hyperaemic sinusoids. This zone was also present in lesions created under the flow condition, although it was not visible on dissection. Hepatocytes outside this area had a normal appearance, but with dilated sinusoids.

Discussion

In this study the influence of hepatic blood flow on the coagulated volumes produced by interstitial laser coagulation in the liver was investigated. Occlusion of the portal flow substantially increased the area of thermal necrosis. In this way intrahepatic lesions 4–5 cm in diameter could be produced in an *in vivo* porcine model.

In these experiments, the size of the lesion under the flow condition was only about 20 per cent of that produced under partial flow and no-flow conditions. Recent computer simulations by Roggan and Muller[16] are consistent with the experimental results presented here. These authors calculated that the coagulation area created with one fibre in a perfused liver would be only 10 per cent of that in a non-perfused liver. Tranberg *et al.*[9] used clamping of both hepatic artery and portal flow in their series of 12 patients treated at laparotomy, based on the supposition that hepatic perfusion would have a lesion-reducing effect. This study provides a rationale for their assumption.

Under partial flow and no-flow conditions, a synergistic effect between the four fibres occurred, leading to fused coagulated lesions of approximately 30 cm^3. This result is comparable to that found in the *ex vivo* situation[15]. The

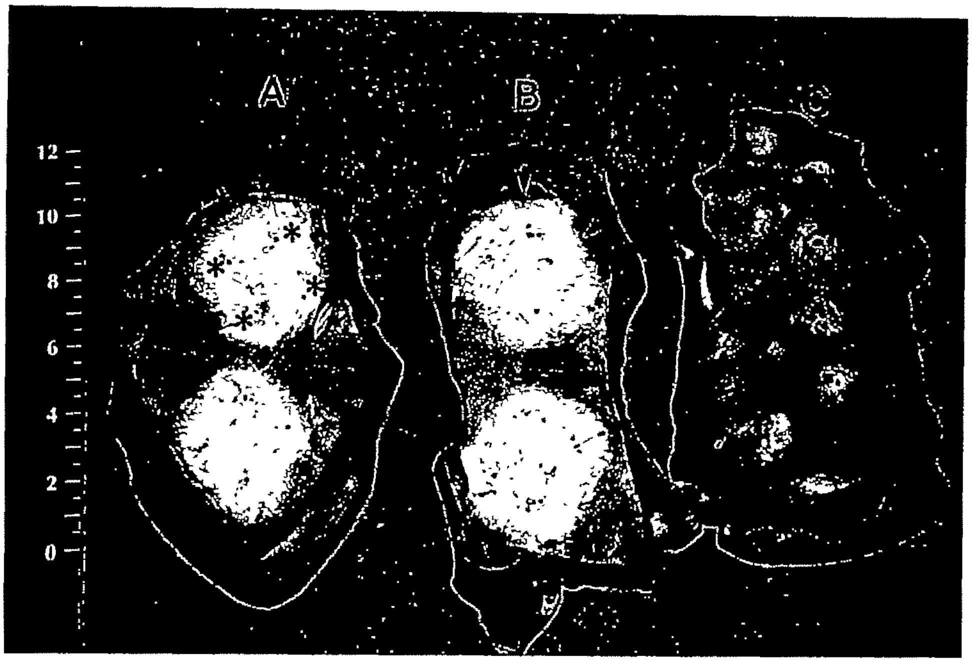

Fig. 1 Macroscopic view of lesions produced under the three experimental flow conditions, showing the largest sectioned planes perpendicular to fibre insertion, with (A) both hepatic artery and portal vein clamped (no flow), (B) portal vein clamped (partial flow) and (C) physiological flow through the liver (flow). Asterisks at A mark the insertion sites of the four fibres; arrows indicate the haemorrhagic rim surrounding the lesions at A and B. All laser applications were performed with four fibres simultaneously using 5 W per fibre for 6 min

Table 1 Characteristics of lesions produced by interstitial laser coagulation in the liver, with four fibres applied simultaneously (5 W per fibre for 6 min)

	Flow ($n=9$)	Partial flow* ($n=8$)	No flow† ($n=6$)
No. with fusion	0	8	6
Height (cm)‡	2·2 (1·6–3·1)	2·9 (3·0–4·0)	3·0 (2·9–3·2)
Width (cm)‡	1·2 (0·5–2·1)	4·5 (4·3–5·1)	4·1 (4·0–4·5)
Volume (cm^3)‡§	6·4 (1·1–12·6)	30·6 (24·6–48·6)	26·6 (19·5–34·5)

‡Values are mean (range). *Portal vein occluded, †portal vein and hepatic artery occluded. §Volumes of non-fused lesions were summed

synergism between the four simultaneously applied fibres is probably caused by the reduced heat dissipation in the area between the fibres. Under the flow condition, however, fusion never occurred and four separate, symmetrical, zones of coagulation were found. Furthermore, the zones surrounding each fibre were smaller than in the *ex vivo* situation. The explanation for this reduction in lesion size by hepatic blood flow is probably twofold. First, the NdYAG light is absorbed by the haem in the erythrocytes[17] and, second, the heat produced is transferred through the vascular system as a result of hepatic blood flow[13,18]. Because of the symmetry of the four separate zones produced under the flow condition, it is proposed that capillary perfusion rather than flow in a nearby large vessel was responsible for the reduction in the size of the lesion. Moreover, selective preservation of tissue surrounding large vessels was not found in this study.

In contrast to the findings in this study, Steger *et al.*[12] reported fused lesions with hepatic flow in canine liver. This observation may be explained by the smaller mutual fibre distance used in their study (1·5 cm compared with 2 cm), allowing overlap of the lesions produced by each fibre. In addition, the amount of cooling by blood flow in the smaller canine liver is much less than that in the porcine liver. The 2-cm distance between fibres was chosen on the basis of one previous study in *ex vivo* liver[15].

No difference was found between clamping of both portal vein and hepatic artery or of portal vein alone. These results express the large difference in arterial and portal flow in both normal and metastases-bearing liver[19]. Although it is generally assumed that hepatic metastases are supplied mainly by the arterial branch[20], clamping of both hepatic artery and portal vein is unlikely to be needed in the clinical situation. The poorly organized vascular bed in the tumour will probably cause only minimal tissue cooling[21]. Particularly in the often ischaemic centre of the tumour, little extra effect can be expected from eliminating the portal flow. The tumour, however, is surrounded by well perfused liver parenchyma, in which the cooling effect is exerted, as found in this study. Therefore, eliminating portal flow should enable the destruction of the vital rim of the tumour and a margin of normal liver tissue. As the net differences in optical properties between liver and tumour are negligible[22], no differences are to be expected in the magnitude of the thermal effect between these two. Indeed preliminary results of experiments with interstitial laser coagulation in human hepatic metastases show areas of coagulation of tumour and surrounding liver tissue similar to those in this study.

The microscopic findings are in concordance with previous studies[12,23,24]. Thomsen[25] also described the peripheral haemorrhagic zone surrounding the coagulated tissue. As dilated sinusoids were found even outside this zone, cells in this haemorrhagic rim are unlikely to survive. However, further research in this field is needed to elucidate the exact correlation between histological findings and tissue viability. Experiments with various immunohistochemical stainings are in progress.

The procedure described here requires a laparotomy. This approach is suitable for patients with irresectable hepatic metastases detected during operation. In addition, it has to be determined whether patients who are considered inoperable because of bilobular involvement may undergo hemihepatectomy when the other metastases are coagulated synchronously and left *in situ*. With advancing radiological and laparoscopic techniques it will eventually be possible to perform the entire laser treatment, including occlusion of the portal vein, percutaneously[26,27]. This will require reliable detection of intrahepatic metastases, combined with online monitoring of the induced tissue coagulation. In this respect, the use of magnetic resonance thermography, based on the temperature-dependent water proton resonance frequency, is promising[28,29].

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Microangiopathy in acute acalculous cholecystitis

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Background Acute acalculous cholecystitis is a well recognized complication of many acute illnesses. Ischaemia of the gallbladder seems to have an important role in its pathogenesis.

Methods Microangiography was performed in 15 gallbladders immediately after cholecystectomy by infusing 10 per cent barium sulphate into the specimen. Five patients had symptomatic gallstone disease, five had acute gallstone-associated cholecystitis and five had acalculous cholecystitis. Sections for histological examination were taken from adjacent sides of the microangiography section. Filling of the vessels by contrast medium was compared with histological findings.

Results Microangiography of the gallbladder in acute gallstone-associated cholecystitis showed strongly dilated arterioles and regular filling of the capillary network, whereas in acalculous cholecystitis the capillary filling was poor and irregular.

Conclusion Disturbed microcirculation may play an important role in the pathogenesis of acute acalculous cholecystitis.

Acute acalculous cholecystitis is not common, representing only 2–12 per cent of all cases of acute cholecystitis in the general population[1,2]. However, its course is often complicated because of necrosis and perforation of the gallbladder. The most common cause of acute cholecystitis is gallstone disease, although in the intensive care unit (ICU) fewer than 15 per cent of cases of acute cholecystitis are associated with gallstones[3]. Acalculous cholecystitis has been shown to be associated with several clinical conditions, all of which may require prolonged intensive care. It has been found to occur in patients with multiple trauma, hypovolaemic shock and septic shock. Acalculous cholecystitis has also been found in association with parenteral nutrition, mechanical ventilation and the use of narcotic analgesics[4–6]. Biliary stasis and ischaemia of the gallbladder have been suggested to be the main factors predisposing to acalculous cholecystitis. Although there is increasing evidence of the detrimental role of splanchnic ischaemia, it has been generally agreed that the aetiology of acalculous cholecystitis is multifactorial.

Ischaemia of the gallbladder appears to have an important role in the pathogenesis of acute acalculous cholecystitis[7,8]. Gallbladder arteriography has been used to evaluate the architecture of gallbladder vasculature in acalculous and gallstone-associated cholecystitis[7]. Warren[7] has demonstrated that gallstone-associated cholecystitis exhibits arterial dilatation and extensive venous filling. In contrast, multiple arterial occlusions with absent or minimal venous filling were consistent features of acute acalculous cholecystitis. In the present study, the findings of gallbladder microangiography were compared with corresponding histological changes in patients with acute acalculous and gallstone-associated cholecystitis, and in those with gallstone disease without coexisting cholecystitis, who served as a control group.

Patients and methods

Microangiography was performed on 15 gallbladders immediately after cholecystectomy. Five patients (mean(s.d.) age 63·8(10·5) years) were operated on electively because of symptomatic cholelithiasis without any clinical or laboratory evidence of acute cholecystitis. In five patients (mean(s.d.) age 56·8(22·3) years) urgent cholecystectomy was performed because of acute gallstone-associated cholecystitis. In the other five patients requiring urgent surgery (mean(s.d.) age 56·4(14·7) years), the diagnosis of acalculous cholecystitis was made in the ICU. Clinical details of the patients with acalculous cholecystitis are presented in *Table 1*. The mean(s.d.) time between admission to the ICU and cholecystectomy was 18·8(5·8) days. The patients were ventilated mechanically because of concomitant respiratory failure. Vasoactive drugs were needed in the majority of patients: one patient received noradrenaline and one dopamine for septic shock, and one patient received dobutamine and sodium nitroprusside for inadequate cardiac output. Nutrition was given enterally, whenever possible.

Gallbladders were investigated immediately after cholecystectomy. Specimens for histological and microangiographic examinations were taken from the areas showing the most severe macroscopical signs of inflammation. The method of microangiography used in this study has been described earlier by Kormano[9]. The cystic artery was cannulated and 10 per cent barium sulphate (Micropague; Nicholas, France) was infused using a pressure of 100 mmHg for 15 min. The gallbladder was then sliced and fixed in a buffered formaldehyde solution, embedded in paraffin wax and sliced at 500 μm for microangiographic studies. Neighbouring slices (5 μm) on both sides of the microangiography section were prepared for histological examination and stained with haematoxylin and eosin. Three to six microangiography slices were taken from each gallbladder specimen and radiographed in contact with a tungsten anode and beryllium window. The focus to film distance was 53 cm, and exposure values were 18 min, 40 kV and 20 mA.

Table 1 Clinical details of patients with acalculous cholecystitis

Patient no.	Age	Sex	Case history
1	50	M	Emergency coronary bypass grafting, respiratory failure, septic shock
2	65	M	Staphylococcal spondylitis with septicaemia
3	34	M	Traumatic rectal perforation with septic shock
4	62	M	Multiple trauma with hypovolaemic shock, respiratory failure
5	71	M	Emergency coronary bypass grafting, respiratory failure

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Results

The gallbladder specimens were macroscopically normal in patients who had undergone elective cholecystectomy. Histological examination revealed mild chronic cholecystitis in each specimen. In three patients with acute calculous cholecystitis, necrosis was observed both macroscopically and histologically. The remaining two patients had cholecystitis with no necrosis either macroscopically or histologically. In the patients with acalculous cholecystitis, there were areas of necrosis in four gallbladders, and in one case the gallbladder revealed cholecystitis without necrosis on both macroscopic and histological examination.

Microangiography of the gallbladder of patients who had undergone elective cholecystectomy revealed regular networks of arterioles and capillaries in each patient. The vessels were well filled and there were no unfilled areas in the capillary network (*Fig. 1*). Microangiographs of these specimens served as reference studies. In gallstone-associated cholecystitis, microangiography of the gallbladders revealed strongly dilated arterioles and capillaries, even though some gangrenous areas were found on histological examination. The vessel network was also more dense in these cases than in the reference cases (*Fig. 2*). In acute acalculous cholecystitis, there was a poor and irregular capillary network in each specimen, although some arterioles were well filled with contrast medium (*Fig. 3*).

Discussion

The main finding of this study was that gallbladder microangiographic findings in acute acalculous cholecystitis were clearly different from those in gallstone-associated cholecystitis, even though the macroscopic and histological findings did not differ significantly between the groups. Microangiography gives structural and qualitative information about the microcirculation of an organ[9,10]. Microangiographs of acute acalculous cholecystitis exhibited deficits in the microcirculation of the gallbladders.

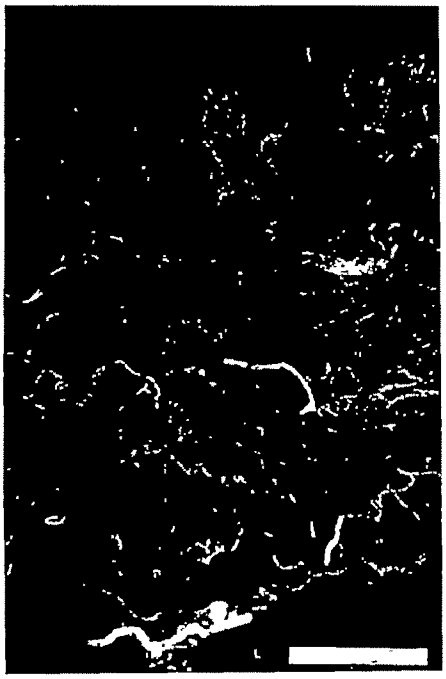

Fig. 1 Microangiograph of the gallbladder in elective cholecystectomy reveals a regular network of arterioles and capillaries. White bar represents 1 mm

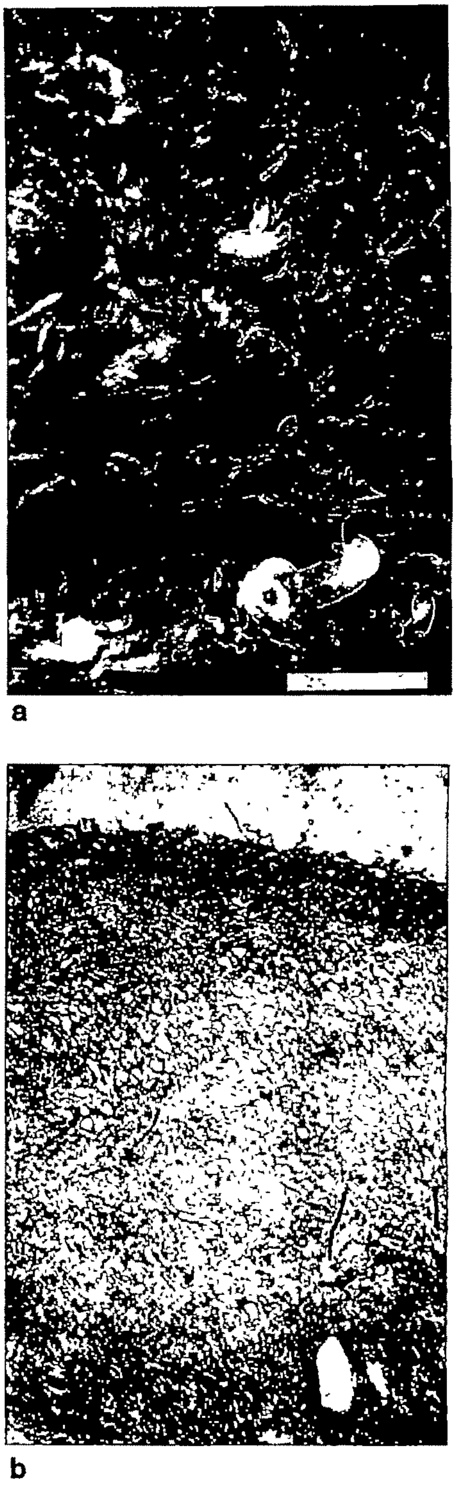

Fig. 2 a Microangiograph in acute gallstone-associated cholecystitis with dilated arterioles and dense capillary network. White bar represents 1 mm. b Adjacent haematoxylin and eosin-stained section shows totally destroyed mucosa and partly necrotic muscular layer of the gallbladder wall

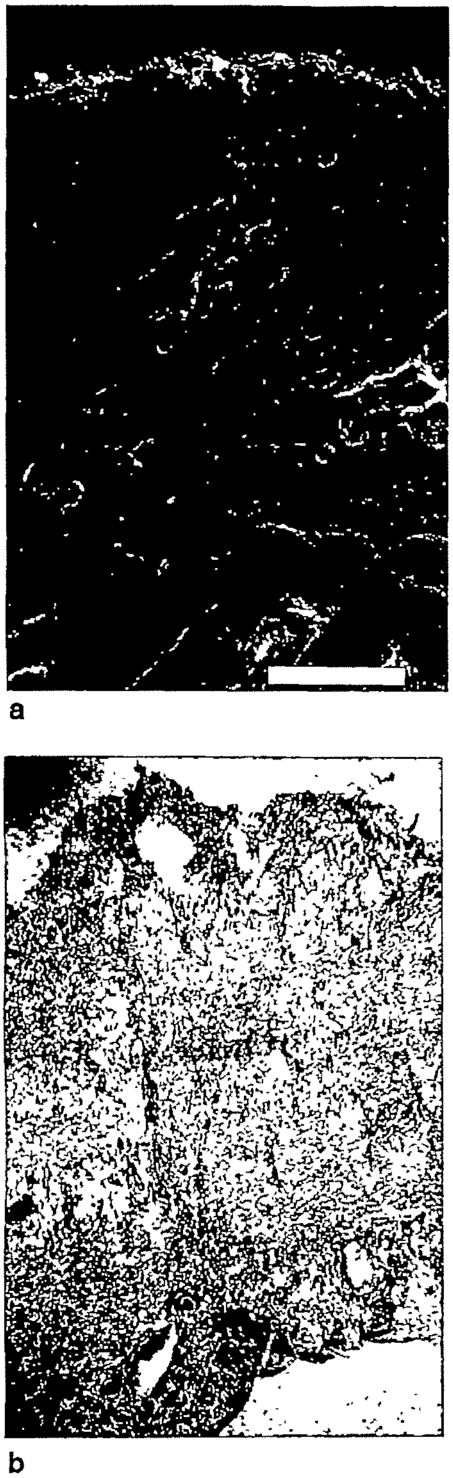

Fig. 3 a Typical microangiograph in acute acalculous cholecystitis. There is irregular filling with contrast medium and areas of unfilled capillaries and arterioles. White bar represents 1 mm. b Adjacent haematoxylin and eosin-stained section illustrates severely necrotic mucosal and muscular layers of the gallbladder wall

The main pathophysiological event for acute gallstone-associated cholecystitis is believed to be obstruction of the cystic duct[11]. Microangiographs of the gallbladders in gallstone-associated cholecystitis revealed a luxuriant microcirculation, which may be related to the inflammatory action. Even though there were necrotic areas on histological examination, several arterioles were dilated and the capillary network was regular in the microangiographs.

Ischaemia is suspected to play a central role in the pathogenesis of acute acalculous cholecystitis[7,8]. Because the gallbladder possesses a terminal artery, it is susceptible to acute ischaemia during an acute low-flow state, particularly in the splanchnic region. Most often acalculous cholecystitis occurs in patients who have suffered from hypovolaemic shock, multiple trauma or septic shock, or in those who have had major surgery[11–16]. Acute acalculous cholecystitis has also been found to be a complication after cardiopulmonary bypass[17–19]. In the present study one patient had suffered multiple trauma, two patients had had septic shock, and the other two had had emergency open heart surgery. All of them had prolonged stays in the ICU.

It has been shown in experimental studies that severe gallbladder ischaemia followed by reperfusion causes acalculous cholecystitis in dogs[20]. The most severe histological changes were seen 2 weeks after the ischaemic attack[20,21]. In the present study, each patient with acute acalculous cholecystitis had a history of circulatory shock 2–4 weeks before the diagnosis of acalculous cholecystitis was made, whereas the circulatory status was normal with patients who had been operated on for gallstone disease or for acute gallstone-associated cholecystitis.

This study suggests that disturbed microcirculation of the gallbladder may play a role in the pathogenesis of acute acalculous cholecystitis. Moreover, the authors believe that acute acalculous cholecystitis may be a misnomer, and that a more accurate term would be 'acute ischaemic cholecystitis'.

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Surgical workshop

Rouvière's sulcus: a useful landmark in laparoscopic cholecystectomy

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Laparoscopic cholecystectomy is now the preferred treatment for gallbladder stones in most major centres. However, the laparoscopic perspective and two-dimensional image of video laparoscopy require the surgeon to use new cues and landmarks, unfamiliar in open cholecystectomy, in order to identify biliary anatomy accurately. These difficulties are reflected in the reported increased risk of bile duct injury in laparoscopic compared with open cholecystectomy[1,2].

Various operating strategies have been described to minimize the risk of bile duct injury during cholecystectomy[3], but a common problem in difficult cases is accurate identification of the position of the common bile duct (CBD).

An anatomical landmark is described, which aids in recognition of the plane of the CBD at laparoscopy.

In 1924, Henri Rouvière described a 2–5-cm sulcus, running to the right of the liver hilum anterior to the caudate process, and usually containing the right portal triad or its branches[4]. Couinaud[5] drew attention to the value of the sulcus in providing access to right portal structures in right-sided liver resections and indicated that it was present in 73 per cent of subjects.

The sulcus was recognizable, being either fully ($n = 41$) or partially ($n = 37$) open, in 78 of 100 consecutive patients undergoing laparoscopic cholecystectomy in this hospital. The sulcus was found to indicate the plane of the CBD accurately in each case. An operative cholangiogram was obtained in 67 of the 78 patients in whom a sulcus was present, providing confirmation of the biliary anatomy.

The authors have found the sulcus to be a useful indicator of the appropriate site to commence dissection of the hepatobiliary triangle in laparoscopic cholecystectomy.

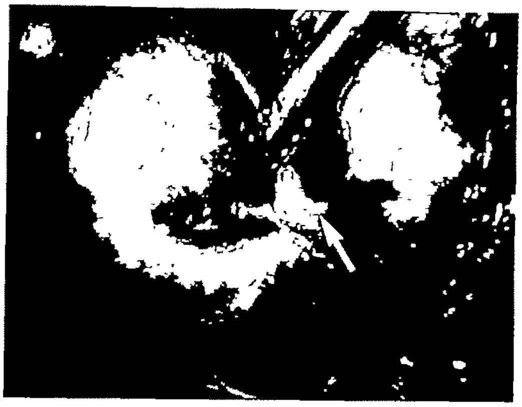

Fig. 1 Partially fused Rouvière's sulcus; the white line of fusion (arrowed) indicates the plane of the sulcus. Dissection ventral to this plane is ventral to the main bile ducts

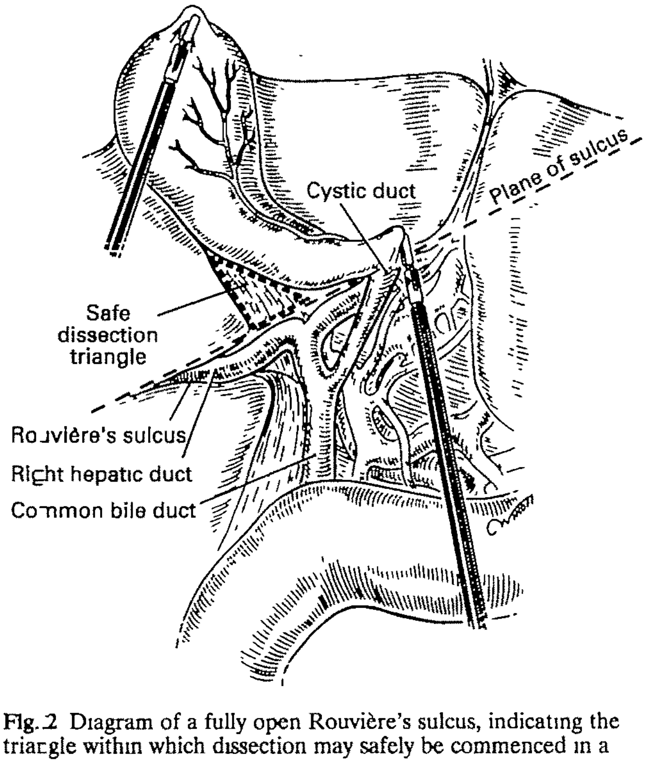

Fig. 2 Diagram of a fully open Rouvière's sulcus, indicating the triangle within which dissection may safely be commenced in a plane ventral to that of the common bile duct

Surgical technique

The sulcus is best seen if grasping forceps are placed on the neck of the gallbladder, which is then retracted upwards and towards the left, so that the posterior aspect of the hepatobiliary triangle is exposed. If present, the sulcus is seen running to the right of the hilum (*Fig 1*). In some patients, the lips of the sulcus are partially fused, with only a small cleft visible laterally.

The sulcus indicates reliably the plane of the CBD; dissection may be started safely by division of the peritoneum immediately ventral to the sulcus and continued in a triangle bounded by the liver surface, the neck of the gallbladder and the plane of the sulcus (*Fig. 2*). Even if the bile duct is tented upwards by the traction that has been exerted on the gallbladder, dissection will be safely ventral to the plane of the duct. Posterior branches of the cystic artery, or a 'caterpillar hump' hepatic artery, may lie in the area of dissection and must be identified with care.

Once a plane has been opened posteriorly, attention may be turned to the anterior dissection, using the posterior landmarks as a guide. The anterior and posterior dissections can then be made to meet, thus opening the hepatobiliary triangle completely.

Utilizing these anatomical principles, the authors have now completed 750 consecutive laparoscopic cholecystectomies, including patients with acute cholecystitis and cases operated on by trainees, without bile duct injury.

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Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy

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Background Postoperative hepatic failure is the leading cause of hospital mortality following hepatectomy for hepatocellular carcinoma (HCC). This prospective study was performed to identify the best test for assessment of the adequacy of hepatic functional reserve in patients with HCC before hepatectomy.

Methods Between April 1989 and June 1993, 127 patients with HCC underwent hepatectomy. Each patient was evaluated before operation with the indocyanine green (ICG) clearance test, the aminopyrine breath test and the amino acid clearance test.

Results Fourteen patients (11 per cent) died after hepatectomy. ICG retention at 15 min showed significant differences between patients who survived or died. By discriminant analysis, the safety limit of ICG retention at 15 min for major hepatectomy was 14 per cent and the relative risk of hospital mortality was 3.

Conclusion The ICG clearance test, expressed as the percentage of ICG retained at 15 min, is the best discriminating preoperative test for evaluating hepatic functional reserve in patients with HCC before hepatectomy.

Hepatectomy offers the best hope of cure in patients with hepatocellular carcinoma (HCC). Even with advances in surgical technique and perioperative care, hepatectomy is still associated with significant morbidity and mortality rates, particularly in patients with underlying chronic liver disease[1,2]. The major cause of hospital mortality is postoperative hepatic failure, which is often preceded by significant intraoperative blood loss or postoperative septic complications. Selection of patients for hepatectomy is conventionally based on Child–Pugh grading, which was originally designed for prognosticating patients with portal hypertension undergoing shunting operations. In recent years, the indocyanine green (ICG) clearance test has been used to assess dynamic hepatic function but the recommended safety limit for hepatectomy has varied among different series[3–6]. Other sophisticated tests such as the amino acid clearance test[7] and the aminopyrine breath test[8] have been evaluated but have not been compared with the ICG clearance test in clinical application. This prospective study was performed to compare the ICG clearance test, aminopyrine breath test and amino acid clearance test in predicting postoperative outcome in patients with HCC undergoing hepatectomy.

Patients and methods

Between April 1989 and June 1993, 127 patients with HCC underwent hepatectomy in this department. The age of the patients ranged from 28 to 79 (median 54) years; the male:female ratio was 112:15. Each patient was evaluated before operation by standard liver biochemistry, Child–Pugh grading, ICG clearance test, amino acid clearance test and aminopyrine breath test. All the data were collected and analysed prospectively; values are expressed as median (range).

Statistical analysis was performed with the help of computer software (SPSS/PC+; SPSS, Chicago, Illinois, USA) The Mann–Whitney *U* test was used to compare continuous variables. $P \leq 0{\cdot}05$ was considered statistically significant. Discriminant analysis was then employed to identify the cut-off value for significant parameters that can maximally separate patients with and without hospital mortality.

Indocyanine green clearance test

ICG is a dark bluish-green tricarbocyanine dye. It is non-toxic, completely and exclusively removed by the liver, and excreted into the bile without intrahepatic conjugation or enterohepatic circulation. After an overnight fast, ICG at a dosage of 0·5 mg per kg body-weight was rapidly injected into the antecubital vein. Blood samples were drawn from the contralateral antecubital vein before the administration of ICG to obtain a blank plasma sample and at 5, 10, 15 and 20 min after injection of ICG. The blood samples were put into heparinized tubes and centrifuged. The plasma samples obtained were read against the plasma blank at 805 nm by a spectrophotometer and concentrations were determined from the standard calibration curve. The results were expressed as the percentage of ICG retained at 15 min after injection. The control value for ICG retention at 15 min was obtained from 17 normal subjects with a median age of 24 years and a male:female ratio of 12:5. The median value for ICG retention at 15 min in normal subjects was 8 (range 3·5–10·6) per cent.

Amino acid clearance test

This test measures the ability of the liver to remove amino acids in the blood for protein synthesis[7]. After an overnight fast, amino acid solution (Vamin; Kabi Pharmacia, Strangnas, Sweden) was infused intravenously at a rate of 40 ml per h for 18 h. Blood samples were drawn from the femoral artery and vein after the intravenous infusion. The samples were then centrifuged at 4°C and 2 ml of the plasma sample was deproteinated by addition to a centrifuge tube containing 100 mg sulphosalicylic acid. The solution was then ultracentrifuged for 30 min at 4°C. The supernatant was aspirated and its pH adjusted to 2·2 using lithium hydroxide 0·3 mol l^{-1}. The specimen was stored at −70°C. The amino acid concentration was determined by an amino acid analyser (Beckman Instruments, Palo Alto, California, USA).

The central plasma clarance rate of amino acid (CPCR-AA) measures the number of litres of plasma cleared of amino acid

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per minute by the liver and other visceral tissue. CPCR-AA is expressed by the following formula:

$$\text{CPCR-AA} = \frac{K_1\ (\mu\text{mol min}^{-1}\ \text{m}^{-2})}{\text{Arterial plasma concentration of amino acid } (\mu\text{mol l}^{-1})}$$

where K_1 is the total peripheral production of amino acid (principally from muscle) plus the rate of intravenous amino acid infusion. Calculation of K_1 was described fully by Clowes and colleagues[7] in 1984. The mean(s.d.) CPCR-AA in healthy fasted subjects[9] was 45(10) ml min^{-1} m^{-2}.

Aminopyrine breath test

Aminopyrine is a 4-dimethyl-[^{14}C]aminoantipyrine. The reagent used in this test was specifically labelled with radioactive carbon at the 4-*N*-methyl groups. After demethylation in the liver, the [^{14}C]carbon dioxide exhaled provides a quantitative measure of the microsomal function of the liver. In this test, the patient was fasted overnight and was given 2 μCi [^{14}C]aminopyrine orally in 50 ml distilled water. The patient remained recumbent for 2 h and then blew through a straw into a counting vial containing 4 ml hyamine hydroxide–ethanol mixture (1:1 volume) and one drop of phenolphthalein until the pink-coloured solution turned clear, indicating that 2 mmol carbon dioxide had been trapped. After addition of scintillation fluid, samples were counted in a liquid scintillation counter. A constant of 9 mmol per kg per h of endogenous carbon dioxide production was included in the calculation and the results were expressed in terms of percentage of dose administered per hour at 2 h. For normal subjects, the percentage of ^{14}C excreted in [^{14}C]carbon dioxide in 2 h was 7 per cent[10]. Values lower than this were regarded as abnormal.

Results

The Child–Pugh status was grade A in 121 patients and grade B in six. Median values for the ICG clearance test, aminopyrine breath test and amino acid clearance test for each Child–Pugh status group are shown in *Table 1*. The results of the ICG clearance test and aminopyrine breath test for patients with Child–Pugh grade A were significantly different from those of patients with grade B.

Fifty-six patients (44 per cent) developed one or more complications after operation, including chest infection (18 patients), pleural effusion (13), biliary leakage (seven), wound infection (four), intra-abdominal bleeding (four), subphrenic abscess (three), peptic ulcer bleeding (two), wound dehiscence (one), variceal bleeding (one), jugular line sepsis (one), myocardial infarction (one) and intestinal obstruction (one). Comparison of clinical and biochemical data, ICG clearance test, amino acid clearance test and aminopyrine breath test results between patients with and without complications showed that none of the parameters manifested a significant difference.

Fourteen patients died after hepatectomy, a hospital mortality rate of 11 per cent. Of these, nine were due to liver failure. *Table 2* shows the preoperative and intraoperative data of patients who died. Some of the data have been reported in relation to a study of major hepatectomy for HCC[2]. Comparison of clinical and biochemical data between survivors and patients who died showed that the total serum levels of bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase and alanine aminotransferase, and ICG clearance test results demonstrated significant differences, whereas the aminopyrine breath test and amino acid clearance test were not predictive of in-hospital death (*Table 3*). By discriminant analysis, the ICG clearance test was the only powerful factor for predicting death in hospital; the overall cut-off point for ICG retention at 15 min was 16 per cent (*Fig. 1*). Of the 127 hepatectomies, 36 cases were minor and the rest were major, defined as resection of two or more liver segments by classical Goldsmith and Woodburne nomenclature[11]. The cut-off value for ICG retention at 15 min was found to be 14 per cent for major hepatectomy and 23 per cent for minor hepatectomy. The relative risk of death for major hepatectomy was 3 if the

Table 1 Indocyanine green clearance test, aminopyrine breath test and amino acid clearance test results in 127 patients with Child–Pugh status A or B

Test	Child–Pugh grade A ($n = 121$)	Child–Pugh grade B ($n = 6$)	P*
Indocyanine green clearance test (%)	11·5	15·1	0·03
Aminopyrine breath test (%)	4·4	2·8	0·01
Amino acid clearance test (l m^{-2} min^{-1})	0·2	0·3	0·93

*Mann–Whitney *U* test

Table 2 Preoperative and intraoperative data for patients who died

Patient no.	Age (years)	ICG retention at 15 min (%)	Child–Pugh status	Operative procedure	Blood loss (litres)	Cause of death
1	68	17	A	Right extended hepatectomy	2	Liver failure
2	54	29	B	Subsegmentectomy	0·4	Liver failure
3	53	24	A	Right trisegmentectomy	20	Liver failure
4	52	15	A	Right hepatic lobectomy	12	Liver failure
5	60	16	A	Right hepatic lobectomy	8	Liver failure
6	52	13	A	Right extended hepatectomy	4	Liver failure
7	66	29	A	Subsegmentectomy	1	Myocardial infarction
8	59	22	A	Right trisegmentectomy	3·5	Liver failure
9	60	22	A	Left extended hepatectomy	5	Subphrenic abscess
10	79	4	A	Right hepatic lobectomy	1·4	Subphrenic abscess
11	37	6	A	Right hepatic lobectomy	1·8	Early recurrence
12	52	18	A	Right hepatic lobectomy	11	Liver failure
13	62	14	A	Right hepatic lobectomy	1·3	Bronchopneumonia
14	79	29	A	Right hepatic lobectomy	10·5	Liver failure

ICG, indocyanine green

Table 3 Comparison of preoperative data for survivors and patients who died

	Survivors ($n = 113$)	Non-survivors ($n = 14$)	P*
ICG retention at 15 min (%)	11 (3–50)	18 (4–29)	0·008
Aminopyrine breath test (%)	4·4 (1·3–9·6)	4·3 (2·8–8·3)	0·69
Amino acid clearance test (l m^{-2} min^{-1})	0·21 (−1·7 to 4·3)	0·15 (−0·2 to 0·9)	0·35
Albumin (g l^{-1})	42 (31–53)	41 (29–46)	0·40
Total bilirubin (μmol l^{-1})	9 (3–70)	14 (7–32)	0·05
Aspartate aminotransferase (units l^{-1})	59 (17–365)	97 (39–340)	0·02
Alanine aminotransferase (units l^{-1})	53 (9–480)	53 (21–322)	0·90
Alkaline phosphatase (units l^{-1})	116 (44–839)	140 (87–334)	0·05
γ-Glutamyl transpeptidase (units l^{-1})	97 (17–1160)	127 (62–865)	0·02
Platelet count (×10^9 litre^{-1})	183 (63–565)	211 (79–371)	0·70
Prothrombin time (seconds over control)	0·4 (−2·3 to 10·7)	0·3 (−1·8 to 2·9)	0·32
Blood loss (litres)	2·2 (0·3–15)	3·8 (0·4–20)	0·09

Values are median (range). ICG, indocyanine green. *Mann–Whitney U test

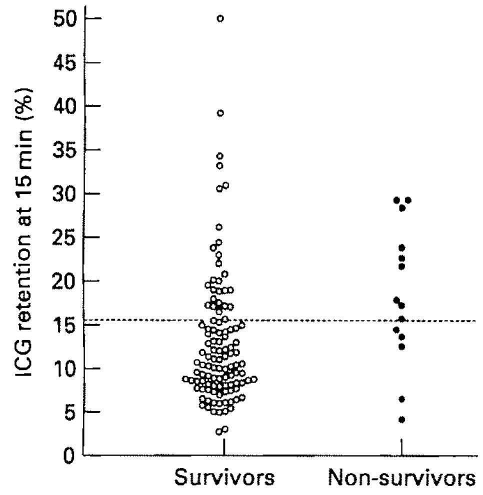

Fig. 1 Distribution of indocyanine green (ICG) retention at 15 min for survivors and patients who died in hospital

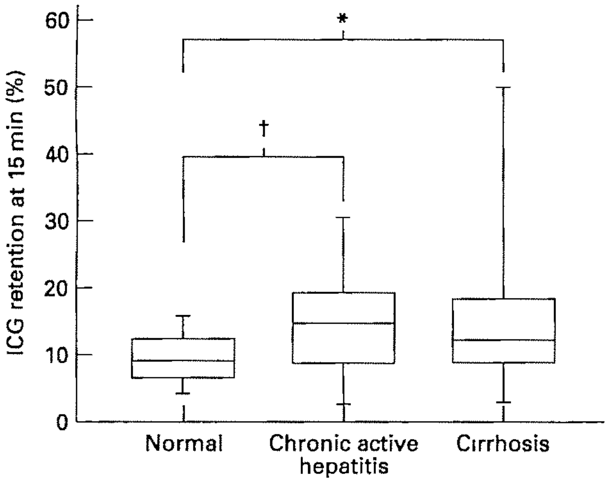

Fig. 2 Boxplot of median (range) values for indocyanine green (ICG) retention at 15 min in 22 patients with normal histology, 30 with chronic active hepatitis and 75 with cirrhotic histology of non-tumorous liver. Whiskers represent the range of ICG retention values. *$P = 0·02$, †$P < 0·01$ (Mann–Whitney U test)

result of ICG retention at 15 min exceeded the recommended value.

The histology of the resected non-tumorous liver was classified into normal, chronic active hepatitis and cirrhosis. The median (range) values for ICG retention at 15 min in each category are shown in *Fig. 2*. The median values for ICG retention at 15 min were significantly different between patients with normal liver ($n = 22$) and cirrhotic liver ($n = 75$) ($P = 0·02$), as well as between patients with normal liver ($n = 22$) and chronic active hepatitis ($n = 30$) ($P < 0·01$). Patients with chronic active hepatitis had the worst liver function in terms of ICG clearance.

Discussion

As hepatic failure is the major cause of death after hepatectomy, various methods have been devised to evaluate hepatic functional reserve. Standard liver biochemistry tests have not been shown to be of any predictive value[12]. Other methods[13,14] have included measurement of uptake of organic anions such as bromsulphthalein, rose bengal and ICG, the oral glucose tolerance test, measurement of arterial ketone body ratio, the aminopyrine breath test and the amino acid clearance test. These tests measure different aspects of hepatic function and may not correlate with one another. The ability of the liver remnant to regenerate, even in a mildly cirrhotic liver[15], also makes correlation of postoperative outcome with preoperative hepatic function test results difficult.

This study demonstrated that the ICG clearance test is the best discriminating test. A wide range of ICG values was observed in patients with the same Child–Pugh grade, indicating that this classification system provides only a rough estimate of hepatic function in patients with HCC. Coupled with the fact that some patients with Child–Pugh grade A lesions died, the ICG clearance test should be considered a more refined test of hepatic function and could replace Child–Pugh grading in selecting patients for hepatectomy. This study also demonstrated a significant difference in ICG values among patients with underlying cirrhosis, chronic active hepatitis and normal liver, but a major overlap of values was present among the three groups of patients with different underlying liver histologies. The ICG clearance test could not therefore serve to differentiate patients with underlying cirrhosis or normal liver, especially at the lower range of values. Nevertheless, it showed that nearly normal hepatic function could be preserved in cirrhotic patients, and that surgeons should not deny hepatectomy based on the histology of the underlying liver alone.

The volume of liver remaining after hepatectomy is definitely an important factor in determining survival, as shown by Okamoto *et al.*[16] and Yamanaka *et al.*[17,18], but if the surgeon wants to rely on a single test to select patients for hepatectomy, and resection will be limited to the liver segment involved by HCC, the ICG clearance test is probably the most accurate method. However, the ICG retention value at 15 min should not be viewed as an absolute guideline because the postoperative outcome depends also on meticulous surgical technique and perioperative care[19–21]. For major hepatectomy, ICG retention of less than 14 per cent at 15 min is the authors' recommended value, which is higher than that proposed by Hasegawa *et al.*[22] and consistent with the finding of Yamanaka and colleagues[23]. Minor hepatectomy can be accomplished even if ICG retention at 15 min reaches 23 per cent, but a larger series is required to substantiate the validity of this result as only two patients with minor hepatectomy died in the present study and both had preoperative ICG retention values at 15 min of 29 per cent.

Clearance of amino acid was shown to correlate with hepatic energy production and survival in patients with encephalopathy[24–26]. Pearl *et al.*[27] suggested that the preoperative central plasma clearance rate of amino acid was valuable in predicting postoperative death in patients with cirrhosis. However, it should be noted that their study population mainly comprised patients with advanced cirrhosis, often complicated by variceal bleeding. In contrast, most of the present patients had Child–Pugh grade A status and a few had grade B. This might account for the failure of the central plasma clearance rate of amino acid to prognosticate death in hospital after hepatectomy. The amino acid clearance test was a rather time consuming and complicated procedure which was liable to error. It required almost a day to compute the result for a single patient. Hopefully, simpler modification of measurement of amino acid clearance, as advised by Bianchi *et al.*[28], may be useful in the future.

The aminopyrine breath test has been evaluated extensively in patients with chronic liver disease. Most of these studies were carried out to assess the prognosis of patients with cirrhosis[29] or cholestasis[30]. Its application in predicting surgical risk is limited. Horsmans *et al.*[31] suggested that the aminopyrine breath test might be helpful in selecting patients with cirrhosis for shunt operation. However, Zahlten[32] and Perri *et al.*[33] pointed out that [^{14}C]carbon dioxide formation did not directly reflect the aminopyrine *N*-demethylation rate by hepatic microsomal enzyme P450. The biochemical pathway that governs formaldehyde and formic acid oxidation to carbon dioxide is highly complex. The carbon dioxide excretion curve is subject to interference by a number of factors, including gastrointestinal motility and basal metabolic rate. The reliability of the aminopyrine breath test in assessing liver function is therefore equivocal. Interpretation of the result must be cautious. Gill *et al.*[34] found that surgery in patients with an abnormally low value on aminopyrine breath testing (less than 2·3 per cent) had an extremely high mortality rate. However, in the present series there were eight patients with aminopyrine breath test results lower than 2·3 per cent but none of these died after operation. Hence, the aminopyrine breath test is not suitable for preoperative assessment of patients with HCC. In accordance with the present findings, Fan *et al.*[35] also demonstrated that the aminopyrine breath test was not useful in predicting outcome in patients with malignant biliary obstruction.

In conclusion, the ICG clearance test, expressed as the percentage of ICG retained at 15 min, is the best discriminating preoperative procedure for evaluating hepatic functional reserve in patients with HCC.

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Day-case transfer of inpatients for diagnostic and therapeutic endoscopic retrograde cholangiopancreatography

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Background To use facilities flexibly and efficiently, a diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) service was offered to inpatients from referring hospitals on a day-case basis.

Methods Patients were transferred by ambulance with a nurse escort and returned to the parent hospital after a short period of recovery. The activity of this service was audited.

Results A total of 188 patients (70 men and 118 women of mean age 63·5 (range 22–94) years) were referred, 55 by physicians or geriatricians and 133 by surgeons from 19 hospitals up to 100 miles distant. Some 109 (58 per cent) had jaundice, 12 (6 per cent) cholangitis, seven (4 per cent) acute pancreatitis and 41 (22 per cent) abdominal pain. All patients arrived between 08:30 and 12:00 hours, all but 16 between 09:30 and 11:00 hours, and all but one with an escort; 129 patients travelled less than 10 miles. The mean time spent in the authors' hospital was 5·9 (range 2·2–9·5) h. The mean time spent away from the parent hospital by patient and escort was 7·0 (range 3·5–10) h. Cannulation failed in 12 patients (6 per cent), two with duodenal tumours. Sphincterotomy was performed in 70 cases, mechanical lithotripsy in seven and stents were inserted in 67. Nine patients were admitted, four for percutaneous stent insertion after failed ERCP and three for abdominal pain (one acute pancreatitis); two patients with sepsis and malignancy died after admission to this hospital. After return to the parent hospital, a further patient died following laparotomy for malignancy and five patients developed abdominal pain (three acute pancreatitis).

Conclusion These findings show that short-stay ERCP can be undertaken on transferred inpatients safely and efficiently without adverse effect on success or complication rates.

The endoscopic retrograde cholangiopancreatography (ERCP) service in this hospital has expanded (a phenomenon also observed elsewhere[1–3]) to cater for many patients referred from other hospitals. Although many of these hospitals have their own ERCP service, the authors have a large tertiary referral practice with over 550 procedures performed annually. Approximately 80 per cent of patients come from outside South Manchester and about 40 per cent have already had ERCP elsewhere[2]. *Fig. 1* demonstrates the increase in number of therapeutic procedures, a trend that has been noted in other units[3,4]. If these were inpatients in the authors' hospital, an additional ten beds would be needed every week. To cope with this demand, a service for day-case treatment of inpatients from other hospitals has been established.

This paper reviews the experience with day-case ERCP over a 13-month period.

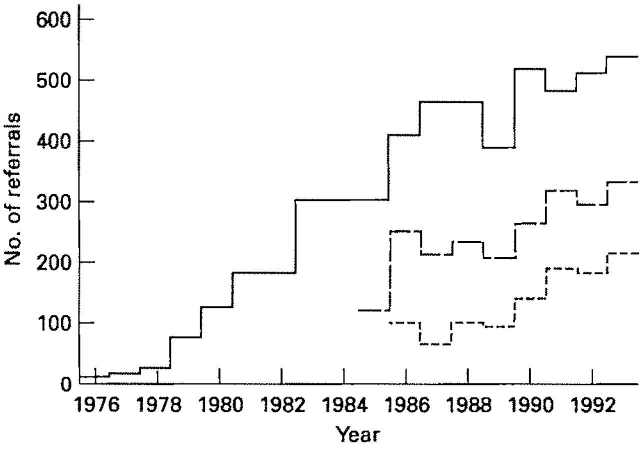

Fig. 1 Graph showing the steadily rising referral numbers for endoscopic retrograde cholangiopancreatography: ———, total; — — — —, therapeutic; - - - - -, stent insertion

Patients and methods

A prospective study was carried out of patients undergoing ERCP as day-case transfers between July 1993 and July 1994 (13 months). A record was made of patients' demographic data, the reason for ERCP and any subsequent procedure, the distance travelled by ambulance, the nurse escort time, the time the patient spent at this hospital, success rates and complications. After referral, staff contacted the appropriate ward of the referring hospital directly to arrange transfer of the patient. An appointment was made (waiting time less than 7 days) and written instructions were sent by facsimile transmission regarding the management of the patient before and after ERCP. For patients who required endoscopic sphincterotomy, provision was made for them to be returned in a supine position in the ambulance. The referring clinician was responsible for assessing the patient's general status and suitability for day-case transfer. It was expected that the referring hospital would arrange nurse escort and ambulance transfer.

On arrival, patients were admitted to the day-case unit. Intravenous access was established and coagulation studies were performed when necessary before transfer to the radiology department. Patients were given intravenous sedation and

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prophylactic antibiotics immediately before the procedure. ERCP was performed by supervised trainees or by experienced endoscopists using standard methods[5]. After completion of the procedure, patients were kept on the day-case unit for observation and a final medical assessment before discharge. Complications and mortality were defined and sought by telephone contact with the referring clinicians after return of the patient.

Results

During the study period 188 patients were referred and were all subsequently accepted for ERCP with the intent of being treated as day-case transfers. There were 118 women (63 per cent). Mean age was 63·5 (range 22–94) years. Fifty-five patients (29 per cent) were referred by physicians or geriatricians and 133 (71 per cent) by surgeons. Patients came from 19 hospitals in the North West of England or North Wales (*Fig. 2*). The longest return trip by ambulance was 200 miles. More than half (109) of the patients had obstructive jaundice, 12 had cholangitis, seven had had previous episodes of acute pancreatitis and 41 had episodes of abdominal pain suggestive of pancreaticobiliary pathology (*Table 1*). Forty-three patients underwent diagnostic ERCP; the remainder had a therapeutic procedure including endoscopic sphincterotomy, mechanical lithotripsy or insertion of a stent (*Table 2*). Nearly all procedures (176 (94 per cent)) were successful but there were 12 patients (6 per cent) in whom cannulation failed and there was one unsuccessful attempt at endoscopic sphincterotomy, which was successfully performed at a further attempt. Of the 12 patients with failed cannulation, two had duodenal invasion by tumour and a further six were deemed to have too low a clinical suspicion of biliary pathology for a further attempt or alternative procedure. These patients were discharged to the parent hospital on the same day. Four patients were kept in this hospital and underwent percutaneous transhepatic cholangiography and a drainage procedure. In addition to these four patients, a further five had to be admitted, one because of unavailability of transport. One developed acute pancreatitis immediately after ERCP, two experienced transient abdominal pain with normal serum amylase levels and one, who was already very ill with cholangitis before the procedure, was considered an inappropriate candidate for day-case transfer and was admitted. Of the two patients who experienced transient abdominal pain, one was discharged to the referring hospital later the same day.

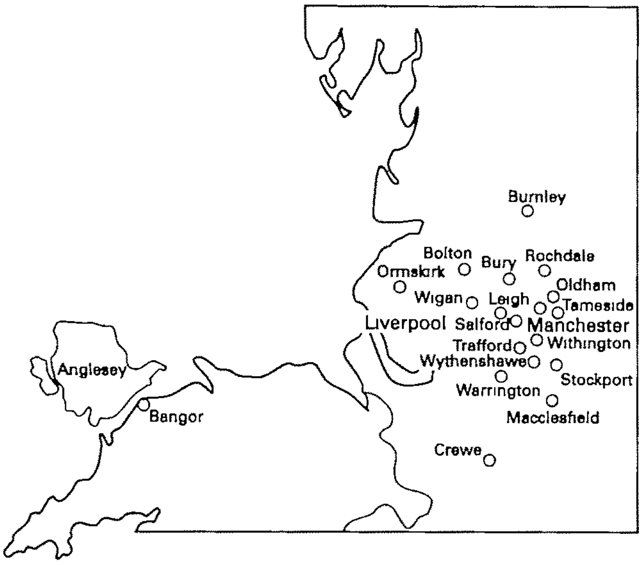

Fig. 2 Map of the North West of England and North Wales showing the location of the 19 referring hospitals

Table 1 Indications for day-case endoscopic retrograde cholangiopancreatography

	No. of patients (*n* = 188)
Obstructive jaundice	109 (58)
Cholangitis	12 (6)
Acute pancreatitis	7 (4)
Abdominal pain	41 (22)
Abnormal liver function	11 (6)
Leak after laparoscopic cholecystectomy	1 (1)
Before laparoscopic cholecystectomy	7 (4)

Values in parentheses are percentages

Table 2 Therapeutic procedures

	No. of procedures	
Endoscopic sphincterotomy	70 (one failed)	
Mechanical lithotripsy	7	
Endoprosthesis		
Pigtail	10	(four failed)
Straight	57	

Mortality and late complications

Three patients died: one with severe cholangitis before ERCP died from unabated sepsis, one with advanced carcinoma of the pancreas, and one suffering from metastatic carcinoma of the pancreas died within 2 weeks following laparotomy at the referring hospital. None died as a direct consequence of ERCP. Five patients who returned to their parent hospital after ERCP developed acute abdominal pain, three had raised levels of serum amylase indicating acute pancreatitis. All recovered with conservative therapy.

Administration and transfer

The median distance for the round trip by ambulance was 14 (range 2–200) miles with 129 patients travelling less than 10 miles. The mean nurse escort time was 7 (range 3·5–10) h and the mean time spent at this hospital was 5·9 (range 2·2–9·5) h. All patients arrived between 08:30 and 12:00 hours, and all but 16 arrived between 09:30 and 11:00 hours. Many took more than 1·5 h to travel less than 10 miles as the ambulance made trips to many hospitals. Although a written request was made at the time of making the appointment that an intravenous cannula should be inserted in the patient's right forearm before transfer, this often had not been done. One elderly jaundiced man was sent in a taxi without nurse escort.

Discussion

Since its introduction in 1968[6], ERCP has evolved from a purely diagnostic procedure to an invaluable tool for the management of biliary and pancreatic disorders[7–11]. Its use has expanded to include patients of all ages[12–14]. Gallstones, pancreatitis and jaundice are commonly encountered in clinical practice and, with the increase in incidence of pancreatic cancer[15], the need for ERCP is rising. It is now the standard method for removal of bile duct stones[16], and the advent of laparoscopic cholecystectomy has increased the demand[17–20]. ERCP is used extensively in the management of malignant obstructive jaundice because it offers relief without operation. ERCP is a particularly attractive option for the elderly for whom an operation would impose an unacceptable risk. Indeed, there is evidence that the number of operations for obstructive jaundice is falling[3].

In 1991, the British Society of Gastroenterology concluded that the need for ERCP services for a district general hospital would be in the order of one per 2000 population. Thus a hospital serving a population of 250 000 would undertake 125 ERCPs per annum[21]. However, it has also been estimated[3] that, for those over 65 years, the need for ERCP is approximately 200 per 100 000 annually. Indeed, figures from our own and other well established units show that the number of ERCPs is rising towards this estimate[3]. The implications of the increasing use of ERCP in treatment must be tackled in a realistic way if an adequate service is to be maintained and expanded in the future. It is the authors' opinion that short-stay ERCP is a feasible option especially as there is no reduction in success rate (94 per cent) or increase in the number of complications[2,7,22]. This study showed a 2 per cent incidence of acute pancreatitis and a 2 per cent mortality rate. There was no significant bleeding following endoscopic sphincterotomy[23–26]. In one patient cholangitis did not resolve with stenting, but no patient developed cholangitis following ERCP[23,24,27–30], possibly reflecting the authors' policy for routine use of systemic antibiotic prophylaxis in all patients[31] and stenting when duct clearance failed.

There was a failure to treat only nine patients (5 per cent) during day-case transfer. This low figure suggests that the current selection of patients for day-case procedures may be conservative[32], and although patient safety is paramount, it may be that a number of potentially suitable patients are kept in hospital overnight unnecessarily. The benefits of short-stay treatment for the patient referred from some distance are that the patient does not need to be admitted to an unfamiliar hospital and that relatives can visit easily after return to the base hospital. These results should encourage experienced endoscopists to establish such a service in their own hospitals. Improvement in this service may be achieved by better organization of transport and having patients adequately prepared for the procedure. As a result of this study, the authors are now planning to expand their use of day-case transfer ERCP.

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Surgical workshop

Laparoscopic approach to pelvic congestion syndrome

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Chronic pelvic pain is a common complaint in women but in many cases there is no obvious underlying pathological process. Pelvic congestion is a well described but often overlooked clinical condition characterized by vulval and lower limb varicosities associated with symptoms of pelvic discomfort. A laparoscopic technique for the management of this condition is described.

Surgical technique

A pneumoperitoneum is established under general anaesthesia. A 10-mm camera port is introduced through an infraumbilical incision and two further ports, one of 10 mm and one of 5 mm, are placed in the right and left iliac fossae respectively. The peritoneum is divided at the level of the pelvic brim and the ovarian veins which appear large and multiple are defined by a combination of sharp and blunt dissection. Great care is taken to identify and preserve the ureter. It may be distinguished from the ovarian veins by traction on the infundibulopelvic ligament which tents up the vessels. Each tributary is then clipped and divided. The procedure is repeated on the contralateral side. The 10-mm wounds are closed with polydioxanone, with skin closure strips.

Patient 1

A 29-year-old woman developed varicosities of the right leg and vulva during pregnancy. She described premenstrual pelvic discomfort. Duplex ultrasonography revealed prominent distended veins in the right side of the pelvis. A selective ovarian venogram confirmed bilateral pelvic varices (*Fig 1*) which communicated with varicose veins in both thighs. Laparoscopic ligation and division of multiple bilateral varicose ovarian veins was performed with right long and short saphenous ligation. The patient made an uncomplicated recovery with complete resolution of symptoms.

Patient 2

A 30-year-old woman presented with varicose veins of the right long saphenous system extending into the vulva; the condition had developed during pregnancy. She described discomfort in the leg and right side of the pelvis during the 2 weeks before menstruation. At recent laparoscopy she was noted to have distended veins in the right side of the pelvis.

Ultrasonography demonstrated large veins on both sides of the pelvis. Varicography confirmed communication between the varicosities in the right leg and pelvis. The patient had laparoscopic ligation and division of multiple distended ovarian veins on both sides of the pelvis and avulsion of the varicosities in the right leg. On review, she still had an occasional dull ache in the right side of the pelvis but symptoms had greatly improved.

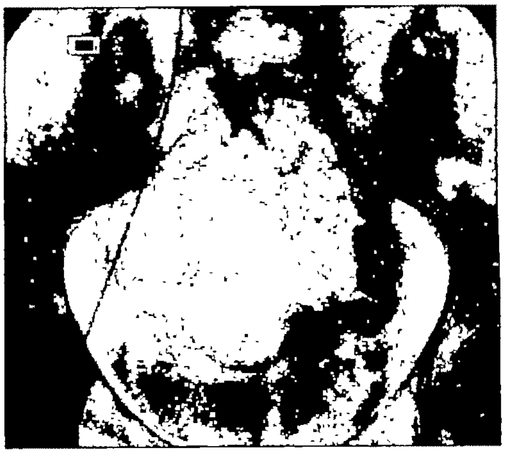

Fig. 1. Ovarian venogram, via a vulval vein puncture, demonstrating varicosities of the left ovarian veins

Discussion

Pelvic pain is the most common indication for diagnostic laparoscopy but in the majority of cases no diagnosis is made[1]. Pelvic varicosities have been described in as many as 91 per cent of women with otherwise unexplained pelvic pain, but the condition can be difficult to diagnose[2]. In women with symptoms, in the presence of varicose veins of the lower limb, ovarian venography should be considered. The condition may be the result of venous compression caused by the gravid uterus producing dilatation and incompetence of the pelvic veins, which is then further exacerbated by erect posture[3].

Occlusion of the ovarian veins by both open surgery[4] and venous embolization[5] can produce prolonged symptomatic relief. The laparoscopic technique described is simple in expert hands and may be useful in ameliorating the symptoms of pelvic congestion.

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Preoperative increase in neuromuscular jitter and outcome following surgery for faecal incontinence

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Background Long-term results of surgery for faecal incontinence remain disappointing. Previous studies have demonstrated that pudendal neuropathy may progress in incontinent patients managed either conservatively or operatively. This progression of pudendal neuropathy may underlie poor long-term results.

Methods Measurement of neuromuscular jitter by single-fibre electromyography allows the stability of terminal motor axons and end-plates to be assessed before operation. An increase in jitter implies progressive denervation.

Results In this study, patients with increased jitter before operation ($n = 14$) had significantly worse symptom scores (median (interquartile range (i.q.r.)) 14 (9–18) *versus* 3 (2–8), $P = 0{\cdot}007$) and lower squeeze pressures (median (i.q.r.) 23 (21–36) *versus* 53 (46–60) mmHg, $P = 0{\cdot}015$) at 6-month follow-up compared with those with normal jitter before operation ($n = 22$).

Conclusion This study implies that the poor results of surgery are related to progressive denervation and that this may be assessed before operation.

Effective management of the patient presenting with faecal incontinence remains one of the most taxing problems for the colorectal surgeon. Sophisticated laboratory and imaging investigations allow the aetiology of the disorder to be determined with a high degree of certainty but optimum management strategies have yet to be defined accurately. Even when guidelines are established the results of surgical intervention can be unpredictable with some patients failing to accrue any benefit while others may show improvement initially only to relapse later.

The authors have attempted to define whether this failure is due to progressive denervation of the pelvic floor. Damage to the innervation of a muscle leads to denervation of individual motor units. It is thought that the denervated muscle fibres produce nerve growth factors that stimulate axonal sprouting from adjacent, intact terminal motor axons. Reinnervation of adjacent, denervated fibres produces the fibre-type grouping seen histologically in the pelvic floor muscles[1] in patients with faecal incontinence. This can also be detected as an increase in mean fibre density in these muscles on single-fibre electromyography[2].

Neuromuscular jitter is defined as the normal variation in interpotential interval between two action potentials recorded from the same motor unit over consecutive discharges[3]. An increase in neuromuscular jitter occurs when terminal motor axons and motor end-plates are immature, and the temporal relationship between activity recorded from individual muscle fibres innervated by the same motor unit is unstable. Measurement of neuromuscular jitter allows the process of reinnervation after denervation to be assessed and is thus an indirect measure of progressive nerve injury. As such it is used by neurologists in the assessment of many disorders of motor nerve conduction[4–8].

Patients and methods

Over an 18-month period, 132 patients were referred for investigation and management of faecal incontinence. All were interviewed in a standard manner by one author (A.S.G.) to establish an accurate history including surgical and obstetric aspects and to numerically evaluate the severity of incontinence using the Cleveland Clinic Score[9]. In this scoring system a score of between 0 and 20 is calculated depending on the frequency of incontinence to solid, liquid stool or flatus, the use of a pad and the frequency of lifestyle alteration. A score of 0 is equivalent to normal continence while 20 represents daily incontinence to solids, liquids and flatus, daily wearing of protective pads and daily lifestyle alteration. After thorough physical examination to exclude local anal or rectal conditions that might have been responsible for the symptom, 118 patients underwent laboratory investigation to elucidate the physiological basis of their incontinence.

All 118 were examined using an eight-channel water-perfused anal manometry apparatus (Narco-Biosystems, Houston, Texas, USA) to determine sphincter length, maximum resting anal canal pressure, maximum squeezing anal canal pressure, anal canal motility and radial asymmetry[10]. Although there are no published series directly comparing vector manometry with endoanal ultrasonography for the assessment of anal sphincter integrity in patients with faecal incontinence, vector manometry is thought to be as accurate as ultrasonography in these patients[10,11] and it has been suggested that endoanal ultrasonography may overdiagnose anterior sphincter deficits in patients whose primary problem is sphincter neuropathy.

Pudendal neuropathy was determined using a St Mark's electrode in conjunction with a Neuromatic 2000 Electrophysiology Unit (Dantec Electronics, Bristol, UK)[12]. The mean fibre density in the external anal sphincter was determined as described elsewhere[2] using a single-fibre electromyography needle in conjunction with the Neuromatic 2000 unit to record the number of linked action potentials detected in a minimum of 20 positions in the external anal sphincter. Jitter software (Dantec Electronics) installed on a personal computer connected to the electrophysiology unit was used to determine neuromuscular jitter. After identifying a motor unit with two or

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more muscle fibres within the recording range of the single-fibre electromyography needle, the mean difference in interval between the action potentials over 200 consecutive discharges of that motor unit was calculated automatically. This is termed the mean consecutive difference. This was repeated in at least ten positions in the external anal sphincter and the mean jitter was calculated. This was completed successfully in 67 of the 89 patients in whom invasive EMG was attempted and in 17 asymptomatic controls of similar age.

For each patient the aetiology of the incontinence was determined, whether their incontinence was primarily due to pudendal neuropathy and denervation of the pelvic floor or primarily caused by traumatic disruption of the anal sphincter by childbirth injury on the basis of history, examination and the results of physiological evaluation. Many patients had evidence of both traumatic sphincter disruption combined with pudendal neuropathy as reported in other series[13]. Those with primarily neuropathic changes were offered a postanal repair whilst those with anterior sphincter deficiency were offered an overlapping sphincter repair combined with levatorplasty. Patients were assessed before operation and at 6 weeks and 6 months after operation.

Results

In 17 asymptomatic control subjects, mean(s.d.) neuromuscular jitter in the external anal sphincter was 27(10) μs. It was therefore taken that a value of greater than 47 μs (mean plus two standard deviations) was abnormal. For practical purposes the upper limit of normal was set at 50 μs which is comparable with that found in other human skeletal muscles[7,14].

Jitter was successfully measured in the external anal sphincter of 67 patients. Thirty-two of these patients had mean neuromuscular jitter of greater than 50 μs. In the 67 patients, jitter was not related to age, pudendal nerve terminal motor latency, mean fibre density in the external anal sphincter, resting anal canal pressure or maximum anal squeeze pressure (*Table 1*). Thirty-six of the 67 patients have now undergone surgery and been followed up for at least 6 months. Twenty-two in this group had normal neuromuscular jitter before operation, while the remaining 14 had abnormally increased jitter. Before operation it was impossible to distinguish between the two groups in terms of age, duration of symptoms, number of vaginal deliveries, pudendal nerve terminal motor latency, mean fibre density in the external anal sphincter, severity of symptoms as assessed by the Cleveland Clinic scoring system, resting or squeezing anal canal pressures, or the relative proportions undergoing overlapping anterior sphincter repair or postanal repair (*Table 2*).

Six weeks after operation, both groups had improved in terms of numerical symptom scores; by 6 months those in the group with increased jitter had deteriorated whereas

Table 1 Relationship between preoperative neuromuscular jitter and other prognostic indicators in 67 patients with faecal incontinence

	r_s	*P*
Age	−0·18	0·076
PNTML	−0·05	0·34
MFD	−0·04	0·38
Maximum squeeze pressure	−0·06	0·31
Mean resting pressure	−0·08	0·27

PNTML, pudendal nerve terminal motor latency; MFD, mean fibre density in external anal sphincter

Table 2 Preoperative comparison between patients with increased jitter and those with normal jitter before operation

	Increased jitter* (*n* = 14)	Normal jitter (*n* = 22)	*P*
Age (years)	57 (46–65)	52 (34–67)	0·58†
Duration of incontinence (years)	5 (3–7)	3 (2–10)	0·43†
Vaginal deliveries	2 (2–3)	3 (2–3)	0·61†
PNTML	2·1 (1·8–2·7)	2·1 (1·8–2·4)	0·75†
MFD	2·1 (2·0–2·6)	2·1 (1·8–2·4)	0·65†
Cleveland Clinic Score	17 (15–19)	15 (13–18)	0·31†
Operative procedure			
Anterior sphincter repair	8	14	0·28‡
Postanal repair	6	8	
Maximum squeeze pressure (mmHg)	36 (28–41)	48 (31–72)	0·08†

Values are median (interquartile range). *Above 50 μs. PNTML, pudendal nerve terminal motor latency; MFD, mean fibre density in external anal sphincter. †Mann–Whitney *U* test; ‡Fisher's exact test

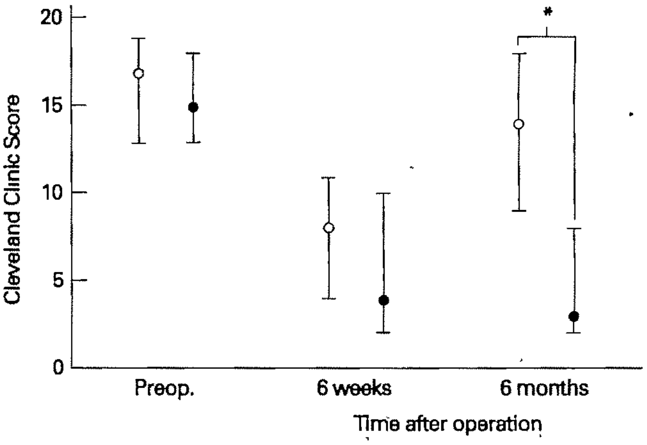

Fig. 1 Change in symptom score with time for patients with increased neuromuscular jitter (○, *n* = 14) or normal jitter (●, *n* = 22) before operation. Values are median (interquartile range). *$P = 0·007$ (Mann–Whitney *U* test)

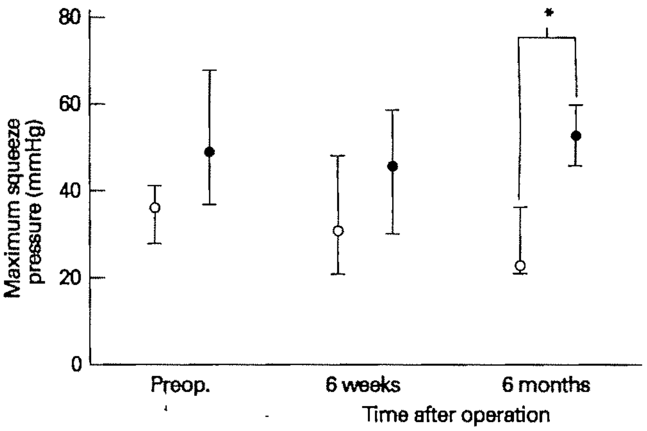

Fig. 2 Change in maximum squeeze pressure with time for patients with increased neuromuscular jitter (○, *n* = 14) or normal jitter (●, *n* = 22) before operation. Values are median (interquartile range). *$P = 0·015$ (Mann–Whitney *U* test)

those with normal jitter had improved further, such that by this point there was a statistically significant difference between the groups (*Fig. 1*). With regard to anal canal squeeze pressures, at 6 weeks after operation there was a drop in maximum squeeze pressure in both groups. In the patients with normal jitter, this decrease was reversed and by 6 months the mean maximum squeeze pressure was greater than preoperative values. In those with increased jitter, there was a further fall in maximum squeeze pressure such that by 6 months there was again a significant difference between the groups (*Fig. 2*).

Discussion

The long-term outcome following surgery for faecal incontinence is poor, with most large series reporting relapse rates of up to 50 per cent[15-20]. It has been demonstrated previously that the outcome following surgery is related to the degree of pudendal neuropathy before operation[9,21] and that pudendal nerve function can continue to deteriorate in a proportion of patients either undergoing surgery[22,23] or managed conservatively[24].

This study has demonstrated that a preoperative increase in neuromuscular jitter is associated with a poor outcome following corrective surgery. An increase in jitter is a measure of immaturity in neuromuscular conduction and implies reinnervation of denervated muscle fibres. It could be argued that an increase in neuromuscular jitter in the acute stage after a nerve injury is a good prognostic indicator as it implies recovery of nerve function. An increase in jitter was observed in one woman in this series within 3 months of a traumatic vaginal delivery; her symptoms improved with non-operative management only. In this situation increased jitter is to be expected and would correspond with the observations of others that spontaneous improvement in symptoms may occur acutely[25]. The remainder of the patients investigated had been symptomatic for a minimum of 2 (median 4, range 2–10) years and an increase in jitter at this stage may be taken to imply progressive nerve injury. These results therefore imply that the poor outcome following surgery for faecal incontinence is related to progressive pudendal neuropathy and that this may be detected before operation.

Faecal incontinence is a spectrum of disease ranging from those with traumatic disruption of normally innervated muscles to those with neuropathic dysfunction of anatomically intact sphincters. Other abnormalities in colonic or rectal function and anorectal sensation may play a key role. Most patients have a combined deficit[13] and, conversely, many women with normal continence postpartum have ultrasonographic evidence of sphincter disruption[26]. Equally, many women with faecal incontinence in whom an anterior sphincter gap amenable to overlapping sphincter repair is found report a traumatic delivery many years previously but have been asymptomatic in the interim. It is therefore apparent that denervation of the external anal sphincter and pelvic floor plays a key role in the aetiology of faecal incontinence and investigation of the anatomical abnormality by either vector manometry[11] or endoanal ultrasonography[27] without investigation of the innervation of the pelvic floor musculature is incomplete.

The presence of combined pathology with variable proportions of direct sphincter disruption and denervation in each patient allows those undergoing overlapping anterior sphincter repair to be combined with those in whom a postanal repair was considered optimal, and the effect of increased jitter in the combined groups to be studied. With the recruitment of more patients to these series it will eventually be possible to produce data regarding the influence of jitter on anterior and postanal repairs independently.

Existing methods of neurological investigation in widespread use such as measurement of pudendal nerve terminal motor latency[12] or needle electromyography[28] give information regarding previous injury but measurement of neuromuscular jitter allows progression of pudendal neuropathy at the time of assessment to be determined. The pathophysiology of pudendal neuropathy remains unclear. It was thought initially to be due to stretch of the pudendal nerves during defaecation straining[29] and childbirth[30] but a recent study has demonstrated that the impairment of conduction is not related to the degree of perineal descent[31] and an alternative explanation must be sought. Furthermore, why 50 per cent of the patients with pudendal neuropathy experience progression of the condition while the remainder appear to stabilize their nerve function is also unclear. It may be argued that those with increased jitter are not suffering from progressive pudendal neuropathy but have failed to recover adequately from a previous injury, such as that sustained at the time of childbirth. In this scenario denervated muscle fibrils stimulate the growth of new terminal motor axons but the resulting new end-plate complex never matures and increased jitter persists. Failure of maturation may be due to lack of specific trophic factors. There is, however, no experimental evidence to support this hypothesis. Some 50 per cent of patients in this study displayed instability of terminal motor axons and end-plates because of either progressive neuropathy or failure to recover from a previous injury as shown by an increase in jitter; this corresponds to the proportion reported as relapsing after treatment or showing evidence of progressive disease when managed conservatively[24].

Needle electromyography of the external anal sphincter is uncomfortable and poorly tolerated. In this series, attempts at recording electrical activity were abandoned in 22 patients because of discomfort and no patient has yet agreed to undertake the examination a second time. Alternative sophisticated methods of detecting neuropathic damage to the pelvic floor and anal sphincters must be developed if further progress is to be made in this area.

Acknowledgements

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Experimental model of pudendal nerve innervation of a skeletal muscle neosphincter for faecal incontinence

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Background Faecal incontinence is difficult to treat. A variety of reconstructive procedures has been described, but none is entirely satisfactory. This study evaluated the feasibility of cross-innervating a skeletal muscle neosphincter with the pudendal nerve in a canine model.

Methods Thirty dogs were rendered surgically incontinent (the pudendal nerve was cut and the external sphincter was partially excised). A neosphincter was then created using the semitendinosus muscle. In ten dogs pudendal nerve transposition (PNT) to the nerve to the semitendinosus muscle was performed. Ten dogs were given a dynamic neosphincter by inserting a pulse generator at 6 weeks. The remaining ten dogs served as controls with passive semitendinosus wraps. Anal manometry was performed before operation and monthly for 5 months. Muscle biopsies, performed at the initial operation and at 5 months, were stained for slow- and fast-twitch fibres, and were examined histologically.

Results At 1 month, mean sphincter function was 32 per cent of the preoperative value in the control animals, 34 per cent in the PNT group and 27 per cent in the electrostimulation group; all dogs were incontinent. At 5 months the mean recovery of sphincter function was 42 per cent of the preoperative value in controls, 100 per cent in dogs with PNT ($P < 0{\cdot}001$) and 63 per cent in dogs having electrostimulation (stimulator on) ($P = 0{\cdot}02$). Six dogs with PNT had squeeze pressures equal to or greater than preoperative levels. At 5 months the ratio of slow to fast fibres was significantly greater in all dogs (control $P = 0{\cdot}01$, PNT $P < 0{\cdot}005$, electrostimulation $P < 0{\cdot}001$).

Conclusion Use of the pudendal nerve to innervate a canine skeletal muscle anal wrap produced a functional anal sphincter that was superior to electrically stimulated and passive wraps.

The electrically stimulated muscle wrap represents the most recent development in skeletal muscle neosphincters for refractory faecal incontinence. Early experience with the electrically stimulated neosphincter has been favourable, but there are obvious limitations to a method that requires insertion of foreign material and which relies on magnet control for continence[1–5]. Innervating a skeletal muscle neosphincter with the pudendal nerve is a step towards a more physiological solution to the complex problem of refractory faecal incontinence. The present study was undertaken to evaluate the feasibility of innervating a skeletal muscle neosphincter with the pudendal nerve.

Construction of an electrically stimulated neosphincter requires several steps. The neosphincter is constructed using either the gracilis or gluteus maximus muscle. The pulse generator is placed at the initial operation or 6 weeks later after healing of the surgical incisions if no stoma is present. The muscle is trained by gradually increasing the degree of stimulation over a period of 2 months. During this training period the patient can expect variable degrees of continence. At completion of the training period the muscle is stimulated continuously and the pulse generator turned off only when the patient wishes to defaecate. In 1995, Baeten *et al.*[1] reported a 73 per cent success rate in 52 patients who underwent dynamic graciloplasty. Patients improved with respect to the median frequency of defaecation (from five to two times every 24 h), median time for which defaecation could be postponed (from 9 s to 19 min) and the median time for which an enema could be retained (from 0 to 180 s).

Techniques of peripheral nerve anastomosis are well described and have changed little over the past three decades[6]. A useful model for nerve repair is the facial nerve which, when injured by trauma, tumour or surgery, often requires grafting. Good to excellent results are achieved using the preferred method of early epineural repair[7,8]. Delayed repair or extensive injury may require the use of transposition grafts (e.g. accessory nerve), microvascular muscle transfers, or an interposition graft (e.g. sural nerve), with less reliable results. The feasibility of cross-innervating a skeletal muscle neosphincter with the native innervation of the external anal sphincter (i.e. the pudendal nerve) was assessed using a canine model of a perineal anal wrap in dogs rendered incontinent surgically.

Materials and methods

The study design compared two treatment groups with one untreated control group. A cross-innervated muscle wrap was compared with a passive muscle wrap (control) and an electrically stimulated muscle wrap. Approval was obtained from the animal care committee at the University of Minnesota for all animal experiments. All animals were housed in accordance with National Institutes of Health guidelines.

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All operations were conducted with the animals under general anaesthesia, induced with sodium pentothal 25 mg/kg intravenously, and maintained by intubation and use of fluorane 2–4 per cent Procedures were performed aseptically and postoperative care was provided in a Research Animal Resources facility under the direction of a veterinary surgeon. An antibiotic (cefoxitin 1 g intravenously) was given before operation and gentamicin 2·0 mg/kg intramuscularly twice daily was given for 1 week after operation. Postoperative analgesia was achieved with buprenorphine 0·003 mg per lb three times daily for the first day and then as required. At completion of the study the animals were again placed under general anaesthesia with endotracheal intubation and then killed with a lethal dose of potassium chloride.

Thirty mongrel dogs were randomly assigned to one of three groups. control, electrostimulation, or pudendal nerve transposition (PNT) All the dogs were rendered surgically incontinent by transection of the pudendal nerve bilaterally and excision of the posterior portion of the external anal sphincter. A 1-cm portion of the nerve was removed bilaterally in dogs in the control and electrostimulation groups, but only on the side opposite nerve transposition in dogs having PNT. A single semitendinosus anal muscle wrap, developed in a previous study, was performed in all dogs[9]. The control group consisted of incontinent dogs with a passive semitendinosus anal wrap and no additional procedures

Dogs assigned to the electrostimulation group returned to the operating room 6 weeks after the initial muscle wrap operation Under general anaesthesia, the leg incision was reopened and the muscle wrap and nerve to the semitendinosus muscle were identified. Two intramuscular leads (Medtronic model SP5577; Medtronic, Minneapolis, Minnesota, USA) were placed, one at a point that produced maximal muscle contraction and the other ground lead 2 cm distal to the first lead, in accordance with the manufacturer's recommendations The pulse generator (Itrel II 7424; Medtronic) was placed in a subcutaneous pocket on the chest wall and the leads were tunnelled subcutaneously to the generator. Before insertion, both the pulse generator and leads were soaked in an antibiotic solution (cefoxitin 1 g in 500 ml normal saline). The muscle was then trained with the same protocol currently in use in a human trial of the electrically stimulated neosphincter. Over an 8-week period, the muscle was stimulated for 2-week periods in a cyclical manner as follows· 0·1 s on, 1·2 s off; 0 2 s on, 1·0 s off, 0·4 s on, 0 7 s off; 1·0 s on, 0·5 s off. At the completion of 8 weeks' training the pulse generator was programmed to stimulate the muscle wrap continuously for 16 h a day. For the remaining 8 h the pulse generator was off to allow the dogs to defaecate.

Incontinence was determined by daily physical examination and the satisfaction of criteria decided by veterinary consultants The presence of a patulous anus, lack of any response to rectal stimulation, and continuous faecal soiling of the perineum and hind legs were required to judge a dog fully incontinent.

The dogs assigned to PNT underwent immediate end-to-end anastomosis between the distal cut nerve to the semitendinosus and the mobilized proximal cut end of the pudendal nerve on that side using interrupted 9–0 non-absorbable sutures with a microsurgical technique (*Fig 1*)

Manometry using a four-channel water perfusion system (Narco Biosystems, Austin, Texas, USA) was performed in conscious dogs before the initial operation to obtain a baseline squeeze pressure and then monthly until completion of the study at 5 months Manometry was performed with the dog standing and the tail in a neutral position. Three separate readings were taken on each dog and the four channels were averaged. Manometric pressure was recorded as the percentage of return to each dog's initial squeeze pressure to reduce individual variation.

The pulse generator in the dogs having electrostimulation was initially programmed at a voltage that produced a 20-mmHg increase in manometric pressure over resting pressure when the muscle was stimulated (usually 1·0–2·0 V). This voltage was subsequently increased as necessary during the muscle training period to maintain the 20-mmHg difference. At the completion of the 8-week training period no further changes in pulse generator settings were made

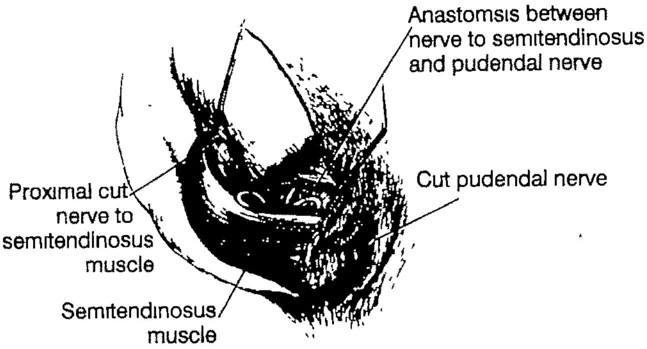

Fig. 1 Pudendal nerve transposition After creation of a semitendinosus muscle wrap around the anal canal the pudendal nerve is anastomosed to the nerve to the semitendinosus muscle

A muscle biopsy of the semitendinosus muscle was obtained at the initial muscle wrap operation and at the end of the study. The biopsies were formalin-fixed and stained with monoclonal antibodies for fast- and slow-twitch fibres (Antiskeletal myosin fast clone My32; Sigma, St Louis, Missouri, USA; Slow muscle myosin MAB 1628; Chemicon, Temecula, California, USA) Fibres were counted using computer-assisted image analysis (CAS200; Becton Dickinson, San Jose, California, USA) Histological analysis consisted of a blind comparison of each pair of haematoxylin and eosin-stained biopsies The slides were graded on a scale of 0–3 (0, none; 1, present; 2, moderate; 3, marked) for the presence of fibrosis, atrophy, hypertrophy and necrosis.

At completion of the study all dogs were returned to the operating room and anaesthetized. The incisions were reopened and all muscle wraps were inspected. The pudendal–semitendinosus nerve anastomosis was identified and the pudendal nerve proximal to the anastomosis was stimulated using an electromyography machine to confirm successful reinnervation of the semitendinosus muscle evidenced by contraction of the muscle A semitendinosus muscle biopsy was taken and the animals were killed without recovery from anaesthesia.

Statistical analysis was performed using a computer statistical program (True Epistat; Richardson, Texas, USA). Manometric findings and histological comparisons were evaluated, first using analysis of variance and then Student's t test for the difference between two means. Fibre typing was analysed with a paired t test to compare the initial and 5-month biopsy results for each group $P<0.05$ was considered statistically significant.

Results

Clinical results

Three dogs had early postoperative wound infections and all were successfully treated with antibiotics. Four dogs had seromas, three requiring percutaneous drainage; all resolved. Two dogs, both from the electrostimulation group, failed to complete the 5-month study. In one dog the nerve to the semitendinosus muscle was injured during implantation of the pulse generator, resulting in a non-functional muscle. The other dog developed perineal cellulitis and sepsis 1 month after implantation and was killed humanely. A pulse generator lead became dislodged in one dog in the fourth week of the 8-week stimulation training period. The operative site was re-explored, the lead replaced, and the dog remained in the study with a 1-week delay in stimulation training.

Two dogs, both in the electrostimulation group, were not rendered completely incontinent. This was noted in the early postoperative period by a return of manometric squeeze pressure and the presence of an anal cutaneous twitch reflex. At the second operation, for placement of the pulse generator, an uncut branch of the pudendal nerve was found in one dog. One week later this dog was excluded from the study because of injury to the nerve to the semitendinosus muscle. Extensive exploration failed to locate an uncut nerve in the other dog, which had a high unstimulated manometric pressure throughout the study.

Digital rectal examinations performed monthly on the dogs correlated with the manometric results. Control dogs failed to regain any anal sphincter tone or ability to squeeze in response to digital examination. The first control dog had a tight wrap and a high squeeze pressure which was consistent throughout the study. Dogs in the PNT group had increased tone on rectal examination and often a return of function was first noted by return of the ability to squeeze in response to digital examination before manometry confirmed the result. Dogs in the electrostimulation group, except the one continent dog, had little tone with the stimulator off and no ability to squeeze on digital examination.

Manometric results

Manometric results for all dogs are shown in *Fig. 2*. Mean preoperative squeeze pressures were similar in the three groups (control 141 mmHg, electrostimulation 144 mmHg, PNT 140 mmHg) as were the pressures 1 month after surgery (control 32 per cent of the preoperative value, electrostimulation 27 per cent, PNT 34 per cent). A significant difference was seen between controls and dogs with PNT at the end of 2 months ($P<0\cdot01$), and the dogs with PNT continued to improve over the 5-month period (*Fig. 2*). At completion of the study, six dogs in the PNT group had full recovery with squeeze pressures equal to or greater than preoperative values ($P<0\cdot0001$). At the end of 5 months the dogs having electrostimulation also achieved significantly greater pressures with the stimulator on ($P<0\cdot05$) compared with control dogs, but the pressures were significantly lower than those for dogs with PNT ($P=0\cdot02$) (*Fig. 2*). In the one dog in the electrostimulation group that was not successfully rendered incontinent, the squeeze pressure with the stimulator off increased to 73 per cent of preoperative value. Three of the dogs having electrostimulation had a drop in stimulation squeeze pressures from month 4 to month 5. Although there was a slight increase in mean squeeze pressure in the control dogs over the 5 months, this was not statistically significant ($P=0\cdot31$).

Muscle biopsy

The initial muscle biopsies had a low percentage of slow-twitch fibres (mean 18–25 per cent), as expected in the semitendinosus muscle (*Fig. 3*). In the second muscle biopsy there was a significant increase in the proportion of slow-twitch fibres in all three groups (mean 50–73 per cent), with the greatest increase in the dogs with PNT ($P<0\cdot001$). Conversion to slow-twitch fibres did not appear to correlate with manometric pressures in either the PNT or electrostimulation groups.

Histological analysis of the muscle biopsies demonstrated varying degrees of fibrosis and atrophy but no evidence of necrosis. Only six of the 30 dogs had evidence of hypertrophy in the postoperative biopsies. Five of these six dogs were controls and one was a dog having electrostimulation. There was a significant increase in the level of atrophy ($P<0\cdot01$) and fibrosis ($P<0\cdot05$) in the PNT group compared with that in controls. There was no significant difference between control dogs and those having electrostimulation or between the PNT and electrostimulation groups.

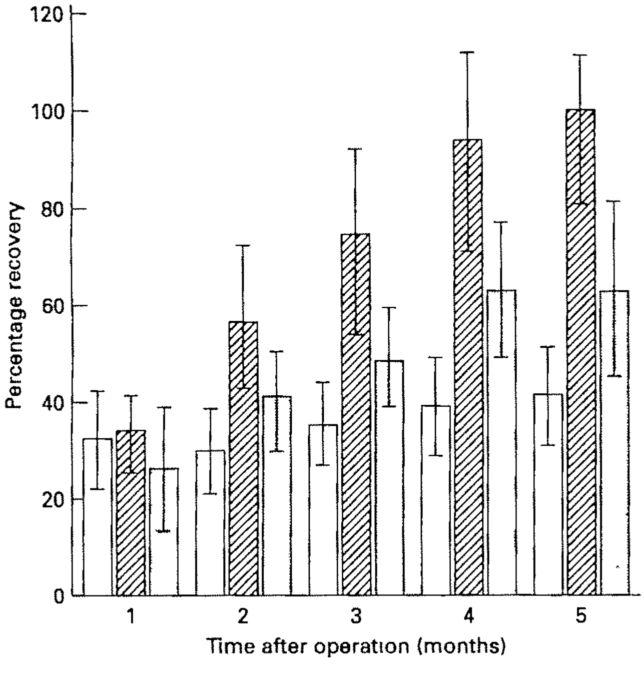

Fig. 2 Manometric results after operation expressed as a percentage of preoperative squeeze pressure Values are mean (95 per cent confidence interval). □, Control, ▨, pudendal nerve transposition; □, electrostimulation

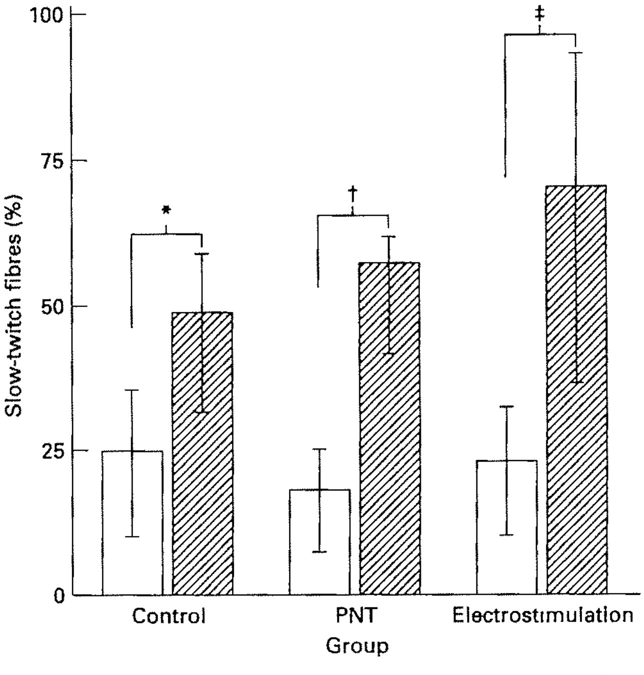

Fig. 3 Muscle fibre typing as seen in biopsies at initial operation (□) and 5 months later (▨) PNT, pudendal nerve transposition $^*P=0\cdot01$, $^\dagger P=0\cdot005$, $^\ddagger P<0\cdot001$ (paired *t* test)

Pudendal nerve function

At the final operation on the dogs with PNT, the pudendal–semitendinosus nerve anastomosis was identified and mobilized, and the pudendal nerve was stimulated proximal to the anastomosis. In all dogs the anastomosis was intact and stimulation of the nerve resulted in contraction of the semitendinosus muscle.

Discussion

There are several obvious advantages to creating an anal sphincter substitute using innervation from the pudendal nerve. This method is more physiological and integrates intact sensory mechanisms. It also avoids the use of a foreign body and the subsequent muscle training necessary for an electrostimulated neosphincter.

The canine model of an anal transposition wrap developed for this study was extremely successful as a chronic model. The dogs tolerated the loss of a leg muscle without any problems. The model also had a low failure rate (two of 30 dogs) and infection rate (three of 30 animals), making it suitable for a study of 5 months' duration. The method chosen to render dogs incontinent was also highly successful, with two initial failures in 30 attempts, one of which was corrected on a second exploration. The control dogs served as effective incontinent controls with consistently low manometric pressures over the 5 months.

It is difficult to determine accurately the continence status of a dog in captivity. Observing cages for evidence of repeated soiling is inaccurate as even continent dogs will stool if confined for long periods. Video recording of the 30 dogs in separate cages, although possibly more accurate, was not performed in this study. Incontinence was determined by strict physical criteria set by veterinary consultants. Control dogs met the criteria throughout the study period and this correlated with their sustained low manometric pressures. Dogs having electrostimulation and PNT also met the physical criteria during the first month of the study. Dogs in the PNT group regained the ability to squeeze in response to rectal examination. Dogs having electrostimulation remained clinically like control dogs when the stimulators were turned off.

The only failures of technique in this study were in dogs having electrostimulation. The second exploration for insertion of the pulse generator and leads resulted in damage to the nerve to the semitendinosus muscle in one dog, and another dog developed perineal cellulitis. An increased rate of infection is not unusual when a foreign body is used in the perineal area and this is also a concern when creating an electrically stimulated neosphincter in humans. In a series of 26 patients undergoing anal dynamic graciloplasty, five had wound infections requiring removal of the device, and the authors pointed out that infection is an important cause of failure with this technique[2]. The injury to the nerve in one dog was a technical error and occurred early in the study, but there is always the potential for morbidity during a second operative exploration near neurovascular structures.

The dogs with PNT had evidence of successful cross-innervation at the end of the second month, and six dogs had full recovery of preoperative manometric pressures by the fifth month. The final mean recovery of 100 per cent of the preoperative value reflects the fact that three dogs had higher manometric pressures at 5 months than before operation. These higher pressures may be attributable to the replacement of the small external anal sphincter with the larger bulk of the semitendinosus muscle.

The results in this study are consistent with those of Shono *et al.*[10]. In that animal study the gracilis muscle was transplanted around the anus with microsurgical anastomoses of the arteries, veins and nerves. Manometric pressure increased 3 months after free gracilis transplantation, with optimum results achieved by 4–5 months The highest level achieved was 81 per cent of the preoperative pressure. More recently, Sato and Konishi have reported successful creation of a functional neoanus in a dog model utilizing transposed biceps femoris muscle with pudendal nerve anastomosis[11]. Their model is similar to the present authors' model in that the muscle is not fully transplanted and only one neural anastomosis is necessary. This approach is technically simpler than complete muscle transfer and can be expected to have lower complication rates and less risk of neosphincter loss.

The dogs having electrostimulation had inconsistent results. Although it was possible to achieve a higher manometric pressure with the stimulator on, the pressures were much lower than those seen in dogs with PNT. During the fourth and fifth months, when the stimulator was on for 16 h per day, manometric pressures increased in four dogs and decreased in three. In humans an increase of 20 mmHg has improved continence[1], and that goal was achieved in five of the eight dogs. In dogs, as in humans, the minimum pressure necessary for continence is unknown. Thus, the pressure levels attained in dogs having electrostimulation, although lower than those achieved by dogs with PNT, may be adequate to maintain normal continence.

Electrostimulation of skeletal muscle can be achieved by direct nerve stimulation or by intramuscular stimulation, as used in this study. Intramuscular stimulation was chosen for several reasons. Intramuscular stimulation is the method used on the authors' patients who are receiving electrostimulated neosphincters. It is also the method most widely used by other investigators[2,3,5]. Direct nerve stimulation has been reported by some centres and has been abandoned by one group after a high incidence of lead problems[12,13]. Improvements in direct neural stimulation may change practice in the future, but intramuscular stimulation is currently the preferred method of many centres using neosphincters.

The increase in the number of slow-twitch fibres in dogs in the PNT and electrostimulation groups was expected as the stimulation to the muscle was altered. The increase seen in the control dogs was less, but still statistically significant. As there was no alteration in stimulation to the control muscles, this result was unexpected, but apparently there was an underlying effect from muscle transposition. Fibre typing of transposed muscle with unaltered innervation is not commonly done, so there are no comparable studies. It is also unclear why the dogs having electrostimulation, despite better conversion to type 1 fibres, had inferior manometric results. This may reflect the underlying limitations of electrostimulated muscle compared with the more physiological pudendal innervated muscle.

Despite the success of pudendal nerve cross-innervation in this study, there are several limitations to the use of this technique in humans. The distance between the pudendal nerve and the neurovascular bundle of a gracilis or gluteus maximus neosphincter may not allow a direct anastomosis. An interposition graft may be necessary (i.e. sural nerve) to bridge the gap. Because the time to reinnervation depends on the distance from the graft to the muscle, human reinnervation would be longer than that seen in this study. This raises the question of how to prevent muscle atrophy in the intervening period. A possible option would be to stimulate the muscle electrically.

Use of this technique in humans would also be limited to patients with a functioning pudendal nerve. This precludes use in the majority of patients with neurogenic incontinence but allows use in traumatic injuries, reconstruction after abdominal perineal resection, and in those with dysfunction of a single pudendal nerve.

In conclusion, pudendal nerve transposition to a semitendinosus anal wrap resulted in a clinically functional anal sphincter superior to a passive wrap or an electrically stimulated wrap. All dogs having the PNT had a significant return of manometric squeeze pressures and the operation was well tolerated with minimal morbidity. Use of the pudendal nerve to innervate a skeletal muscle neosphincter produced a more physiological anal sphincter than existing methods for refractory faecal incontinence. This model warrants further development for adaptation for human use.

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Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening

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Background Published data suggest that screening might reduce the mortality rate from colorectal neoplasia. Faecal occult blood (FOB) testing suffers from poor sensitivity and significant numbers of interval cancers, both of which should be improved by the addition of flexible sigmoidoscopy (FOS).

Methods This prospective, randomized study aimed to assess the compliance and neoplasia yield of FOB testing and FOS compared with that of FOB testing alone. From general practitioner registers, 6371 asymptomatic patients (3124 men, 3247 women; age range 50–74 years) were invited for screening by means of FOB testing (3128 patients) performed at home, or a combination of FOB testing and FOS (3243 patients).

Results Compliance with FOB testing alone was 50 per cent. In the FOB testing/FOS group, 48 per cent returned the FOB test but only 20 per cent went on to FOS. Despite the poor compliance, the neoplasia yield was four times greater in the FOB testing/FOS group.

Conclusion FOS increases the neoplasia yield but strategies to improve compliance must be identified for this to become a population screening test.

Colorectal cancer fulfils many of the criteria making it suitable for population screening[1]. It is a major health problem in the UK with approximately 28 000 new registrations and 19 000 deaths per annum[2]. Despite recent advances in surgical practice[3] and adjuvant therapies[4], the overall 5-year survival rate (35 per cent) has remained little changed as most cases are already at an advanced stage at the time of diagnosis[5]. Support for population screening for colorectal neoplasia has been gathering over the past 5–10 years; the results suggest that a reduction in mortality rate of 33 per cent might be achieved[6]. Faecal occult blood (FOB) testing is the most investigated screening test in several large trials[6–8]. Its disadvantage of low sensitivity could be greatly improved by the addition of flexible sigmoidoscopy (FOS)[7].

Few data are available on compliance with FOS in an average risk population. The aims of this study were to assess both the acceptability and neoplasia yield of FOS in a randomized, prospective study of asymptomatic individuals.

Patients and methods

Asymptomatic individuals aged 50–74 years of age were identified from two general practice registers, one rural practice and one inner city. The general practitioners (GPs) were asked to exclude unsuitable subjects, i.e. those with proven colorectal neoplasia, patients under investigation for abdominal symptoms, those with other advanced disease etc. Those on the edited list were randomized by household using standard random number tables into two groups group 1 was offered FOS and FOB testing; those found to have a positive FOB test or who had neoplasia detected at FOS were investigated further by colonoscopy Group 2 was offered FOB testing only and those with a positive result were further investigated by colonoscopy; those with negative tests had no further investigation.

Both groups were contacted by GP letter which included the FOB tests (Haemoccult; YS1, Farnborough, UK) and instructions for use (no dietary restriction or rehydration of the test). The letter detailed the purpose of FOB testing and a contact number was provided in case of difficulty People in group 1 were also invited to attend the GP surgery on a specified day to discuss a further examination. Two reminder letters were sent to patients who failed to reply. Those subjects who attended the GP surgery were seen by a Research Sister who explained the nature of FOS and arranged a mutually convenient date for the investigation to take place. A single phosphate enema was given as bowel preparation and FOS was performed without sedation.

Results

Over 4 years in Newport, South Wales, 6371 individuals were identified and randomized prospectively to the two groups. No differences were seen in the demographic details of the two groups (*Table 1*).

Compliance with FOB testing was 50 per cent in the FOB testing only group (*Fig. 1*) and 48 per cent in the FOB testing/FOS group (*Fig. 2*). Neither group demonstrated a trend in compliance when assessed for age and sex. Compliance with FOS was only 20 per cent (*Fig. 3*). Analysis of this group highlighted the steps at which non-compliance with FOS occurred (*Table 2*).

The neoplasia yield was determined by the number of

Table 1 Age and sex distribution of the screened population ($n = 6371$)

	FOB testing and FOS	FOB testing
Men	1570	1554
Women	1673	1574
Total	3243	3128
Mean age (years)	61·6	61·4

FOB, faecal occult blood; FOS, flexible sigmoidoscopy

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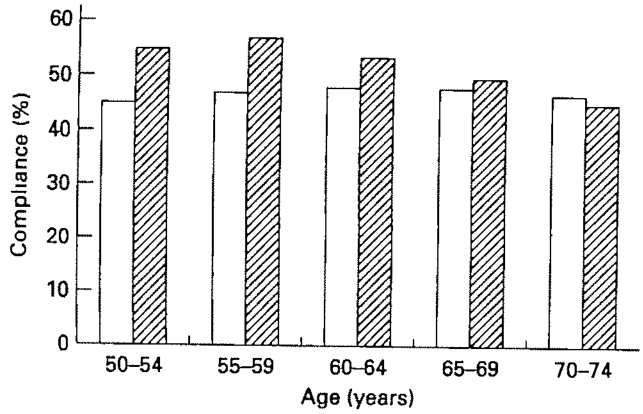

Fig. 1 Compliance with faecal occult blood (FOB) testing by age and sex in the FOB testing only group □, Men; ▨, women

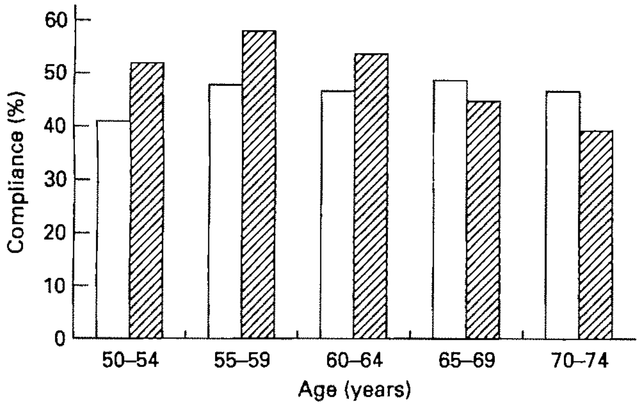

Fig. 2 Compliance with faecal occult blood (FOB) testing by age and sex in the group randomized to FOB testing combined with flexible sigmoidoscopy. □, Men; ▨, women

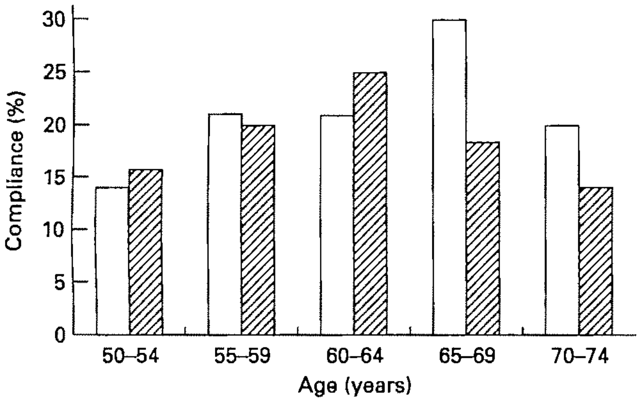

Fig. 3 Compliance with flexible sigmoidoscopy by age and sex. □, Men; ▨, women

Table 2 Compliance with flexible sigmoidoscopy

	No. of patients ($n = 3243$)
Refused FOB testing	1672 (52)
Returned FOB test and accepted FOS	656 (20)
Returned FOB test but refused FOS at GP surgery	416 (13)
Returned FOB test but did not attend for appointment at GP surgery	497 (15)

Values in parentheses are percentages. FOB, faecal occult blood; FOS, flexible sigmoidoscopy, GP, general practitioner

Table 3 Patients detected with significant neoplasia by each investigation

	FOB testing and FOS group		FOB testing only group
	FOB test	FOS	
Adenoma (> 1 cm)	6 (10)	20 (22)	4 (7)
Carcinoma	1 (1)	2 (2)	2 (2)

Values in parentheses are numbers of lesions. FOB, faecal occult blood; FOS, flexible sigmoidoscopy

patients detected with large (greater than 1 cm) adenomas and/or carcinomas (*Table 3*). The results from FOB testing alone were similar in the two groups; seven patients (with 11 lesions) were identified in group 1 and six patients (with nine lesions) in group 2. The seven patients with a positive FOB test in group 1 went directly to colonoscopy; a further 22 patients in this group with a negative FOB test had 24 significant lesions detected by FOS.

FOB testing alone therefore detected 2·0 patients with significant neoplasia per 1000 screened (4·2 patients per 1000 who completed the test). The combination of FOB testing and FOS detected 8·9 patients with significant neoplasia per 1000 screened (44·2 patients per 1000 who completed the tests).

Discussion

Central to the argument for population screening is that approximately 75 per cent of colorectal cancers arise sporadically[9], probably in pre-existing adenomas[10]. A window of opportunity exists for the detection of polyps at a premalignant, and therefore potentially curable, stage. The transition time from the benign to malignant phase is long; the cumulative risk of the diagnosis of cancer in polyps of 10 mm or greater is 8 per cent at 10 years[11]. Furthermore, even if the lesion is malignant at the time of screen detection, these cancers are at a less advanced pathological stage[7] than those which present with symptoms, suggesting a possible survival advantage.

The main disadvantage of FOB testing is its low sensitivity. About 30–40 per cent of cancers and as many as 80 per cent of adenomas may be missed[7,12,13]. The addition of FOS should increase sensitivity and data from three large studies[14–16] all suggest that sigmoidoscopy might reduce the incidence of distal colorectal cancer by as much as 60–85 per cent.

Screening by FOS would therefore seem an attractive proposition but to date few data are available on the subject of compliance with this test in an average risk population. In this prospective, randomized study, compliance with FOB testing in groups randomized to FOB testing only and FOB testing combined with FOS was 50 and 48 per cent respectively, similar to previous rates from the UK[7]. Compliance with FOS was only 20 per cent, considerably lower than that in three previously published series[17–19]. However, the first study used a volunteer population, the second a highly targeted group and the third a high-risk population.

Despite the poor compliance with FOS in this study, the potential of FOS to increase neoplasia yield has been demonstrated. All the lesions detected by positive FOB test in the FOB testing/FOS group were within reach of the flexible sigmoidoscope. Since no additional lesions were detected within 60 cm of the anal verge at colonoscopy following positive FOS, FOS alone would have detected all significant lesions in this group. This observation is supported by data which demonstrate a 96 per cent correlation of endoscopic and pathological findings for polyps of more than 1 cm diameter[20]. The yield of large adenomas by FOS in this study was comparable to that in a previously published necroscopy study in the UK[21].

This study has demonstrated that FOS can significantly increase neoplasia yield but this potential benefit will only be fully realized by identifying strategies to increase compliance with the test. Until the issue of poor compliance is addressed, a 20 per cent compliance with FOS in an average risk population should be used in calculations of potential cost benefits of population screening and potential trial sizes using FOS.

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Anoabdominal rectal resection and colonic J pouch–anal anastomosis: 10 years' experience

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Background Coloanal anastomosis and radiotherapy for the treatment of lower rectal carcinoma have been receiving increasing attention.

Methods Patients with rectal cancer were divided into two groups: anoabdominal rectal resection and colonic J pouch–anal anastomosis (CAA) plus preoperative intraluminal brachytherapy (IBT) (group 1; 68 patients) and CAA without IBT (group 2; 23 patients). Group 3, comprising 59 patients who underwent abdominoperineal excision (APE), was examined as a control group. Comparative results were reviewed.

Results Postoperative complications occurred more frequently in group 1 than in group 2. Actuarial 5-year survival rates were 73 per cent in group 1, 64 per cent in group 2 and 63 per cent in group 3. Cumulative local recurrence rates at 5 years were 11 per cent in group 1, 38 per cent in group 2 and 21 per cent in group 3. Intestinal continuity breakdown was seen in 14 per cent of all patients at 5 years after initial operation.

Conclusion The combination of CAA and preoperative IBT resulted in decreased local recurrence. IBT followed by CAA can be a good restorative option for combating lower rectal cancer.

Coloanal anastomosis was first introduced in 1972 by Sir Alan Parks[1], and involved endoanal anastomosis of the colon to the dentate line within a circumferential muscle cuff. Parks and Percy[2] reported that the long-term survival and local recurrence rates after coloanal anastomosis were similar to those after abdominoperineal excision (APE)[2]. This procedure has been widely used not only for benign and malignant tumours of the rectum but also for rectovaginal fistula[3], haemangioma[4], and radiation proctitis[5–7]. However, both urgency and frequent defaecation often continue to cause problems after coloanal anastomosis. Lazorthes *et al.*[8] and Parc *et al.*[9] incorporated a colonic J pouch which was anastomosed directly to the dentate line, and functional superiority of the colonic J pouch has been reported[10–14]. Modification of the procedure with resection of the internal anal sphincter[15], and anastomosis with intraluminal circular staplers at the upper anal canal have been reported[12–14].

The authors have used anoabdominal rectal resection and colonic J pouch–anal anastomosis (CAA) since November 1985 and found initial satisfactory bowel function. Since October 1986, preoperative intraluminal brachytherapy (IBT) has been administered to patients with lower rectal carcinoma to improve the oncological result after CAA. This report analyses the outcome in 100 patients who had CAA, focusing retrospectively on the destiny of the colonic reservoir and patients' survival.

Patients and methods

Patients

Since November 1985, 67 men and 33 women underwent CAA; mean age was 56 (range 15–83) years. The indication for CAA was rectal cancer in 91 patients. Four procedures were performed for villous tumour, two for benign rectal stenosis, one for radiation proctitis after external radiotherapy for a cervical carcinoma, one for rectal juvenile polyps and one for solitary ulcer syndrome.

Table 1 shows the characteristics of the 91 patients with rectal carcinoma who underwent CAA and who were divided into two groups. group 1 (68 patients) received preoperative IBT, and group 2 (23 patients) did not. Group 3 consisted of 59 patients with rectal carcinoma who underwent APE (from 1978 to 1992) before the introduction of CAA as a historical control. There were no significant differences among the three groups in any parameter except for Dukes classification, as shown in *Table 1*.

Operative procedure

This was performed as described previously[11,15], placing the patient in the prone jack-knife position for the anal approach to

Table 1 Characteristics of patients with rectal carcinoma

	Group 1	Group 2	Group 3
No. of patients	68	23	59
Sex ratio (F:M)	22:46	6:17	21:38
Median (range) age (years)	56 (25–78)	58 (34–78)	62 (30–82)
Median (range) tumour location (cm from the anal verge)	5 (2–11)	6 (3–9)	4 (2–9)
Median (range) tumour diameter (cm)	4 (0–8)	4 (1–12)	4 (1–12)
Differentiation			
Well	34	17	36
Moderately	30	6	16
Poorly	2	0	2
Mucinous	2	0	5
Dukes stage			
A	27*	7	13*
B	11	6	17
C	26	10	27
D	4	0	2
Median (range) follow-up (months)	56 (9–60)	48 (8–60)	57 (11–60)

Patients underwent anoabdominal rectal resection and colonic J pouch–anal anastomosis with (group 1) or without (group 2) preoperative intraluminal brachytherapy, or abdominoperineal excision (group 3) $*P<0{\cdot}05$, group 1 *versus* group 3 (χ^2 test)

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mucosal resection and exposure of the internal anal sphincter and the intersphincteric space[15]. After closure of the rectal stump the patient was turned in the Lloyds-Davies position to allow anterior resection of the rectum with lymphadenectomy. A colonic J pouch 8–10 cm in length was created from the sigmoid colon with linear staplers. Then, with the patient in an exaggerated lithotomy position, the reservoir was anastomosed to the dentate line with interrupted sutures. A diverting ileostomy (sometimes colostomy) was constructed, and closed 3–6 months later.

Preoperative radiation therapy

Sixty-eight patients with rectal carcinoma from whom informed consent was obtained underwent preoperative IBT (group 1) as described previously[16]. Before irradiation, the proximal and distal borders of the tumour were detected by colonoscopy and marked on the skin under fluoroscopic guidance. To protect the perianal skin, a hip shell made of thermoplastic resin ensuring fixation of tubes during radiation was made for each individual patient. The appropriate outer tube, which was selected from three types according to the circumferential rate and macroscopic type of the tumour[17], was fixed to the hip shell and inserted into the rectum. With the patient in the left lateral position, the inner tube was inserted into the outer tube, and the radiation source (cobalt-60 with an activity of 1·7 or 2·6 Ci) was applied. Doses at a point 5 mm below the mucosa were calculated using a computer. Single doses ranged from 10 to 40 Gy, and total doses from 30 to 80 Gy. CAA was performed 2 weeks after IBT.

Functional assessment

Postoperative bowel movement and symptoms were assessed at the time of manovolumetric examination. Patients to be examined manovolumetrically were selected from patients in group 1 treated with moderate-dose IBT (30–40 Gy) and from group 2 without IBT. The methods have been described previously[11,15] and included measurement of anal canal pressure, pouch capacity and pouch distensibility.

Clinical assessment

Clinical check points were (1) postoperative complications, (2) local and distant recurrence, (3) death from cancer, and (4) survival of the colonic J pouch. Postoperative complications were recorded prospectively. Follow-up information was obtained from office charts, hospital records and telephone interviews. Median follow-up was 4·5 years after CAA. Probability curves for local recurrence and survival were generated by the Kaplan–Meier product-limit method[18]. The significance of these curves was compared using Gehan's generalized Wilcoxon test including a Bonferroni adjustment. Characteristics of patients and complications were assessed using the χ^2 test. Functional assessment was carried out by one-way analysis of variance (ANOVA). Statistical significance was assigned to the value of $P<0{\cdot}05$.

Results

There were no hospital deaths in the 100 patients who had CAA. In patients with rectal cancer treated with preoperative IBT (group 1), histology of the resected specimens revealed a change in all cases, and nine tumours were diminished in size. IBT results in downstaging of primary tumours[16,19], and this might explain why group 2 contained a significantly higher number of Dukes A tumours than the other groups.

Complications

The nine patients with benign disease had an uneventful postoperative course. Of the patients with carcinoma, those in group 1 had a significantly higher incidence of complications than those in group 2 (*Table 2*), particularly radiation ileitis and perianal skin problems. Group 1 contained 12 patients given high-dose IBT (40–80 Gy) in whom the incidence of complications was significantly higher than that in the 56 patients who received a moderate dose (30–40 Gy) ($\chi^2=6{\cdot}5$, 1 d.f., $P=0{\cdot}01$). Surgical intervention for complications in group 1 was required in six of the 12 patients who had high-dose IBT and four of the 56 who had moderate-dose IBT ($\chi^2=14{\cdot}5$, 1 d.f., $P=0{\cdot}0001$).

Functional outcome

Both anopouch physiological parameters and symptoms reached a steady state 12 months after stoma closure. *Table 3* summarizes the functional results 12 months after stoma closure. Incomplete evacuation was observed most

Table 2 Complications after anoabdominal rectal resection and colonic J pouch–anal anastomosis in patients with rectal cancer

Complications	Group 1 ($n=68$)	Group 2 ($n=23$)
Septic		
Fistula		
Rectovaginal	5	0
Rectocutaneous	2	0
Anastomotic dehiscence	0	2
Pelvic sepsis	3	3
Small bowel		
Obstruction	5	1
Perforation (ileitis)	2	0
Colonic pouch		
Ischaemic pouchitis	3	1
Colon cast	2	0
Perianal skin	21	0
Miscellaneous		
Anastomotic stricture	3	0
Apical pouch bridge	1	1
Stoma problem	1	0
Bleeding	0	1
No complications	28*	17

Patients underwent anoabdominal rectal resection and colonic J pouch–anal anastomosis with (group 1) or without (group 2) preoperative intraluminal brachytherapy. $^*P<0{\cdot}05$ *versus* group 2 (χ^2 test)

Table 3 Functional results after anoabdominal rectal resection and colonic J pouch–anal anastomosis

Daily stool frequency (per day)	2·0(1·2)
Soiling	7 of 38 patients
Flatus/faeces differentiation	34 of 38 patients
Urgency	1 of 38 patients
Incomplete evacuation	27 of 38 patients
Physiological findings	
Maximum resting pressure (%)*	82·4(12·4)
Maximum squeeze pressure (%)*	86·8(21·6)
Threshold volume (ml)	108·0(36·8)
Maximum tolerable volume (ml)	206·4(65·8)
Distensibility (ml/cmH$_2$O)	3·8(1·4)
Anal canal length (cm)	2·9(0·5)
Anopouch angle (°)†	109·5(11·4)

Values are mean(s.d.). Function was assessed in 38 patients 12 months after operation. *Percentage recovery from control value; †measured between the longitudinal axis of the J pouch and anal canal frequently. Urgency, a troublesome symptom after straight coloanal anastomosis[11], decreased after CAA. Anal canal pressures recovered to over 80 per cent of preoperative values. The maximum tolerable volume of the J pouch was equal to that of the normal rectum (mean(s.d.) 218·8(84·6) ml; $n = 12$). Mean(s.d.) threshold volume and distensibility of normal rectum were 106·6(36·4) ml and 3·0(0·8) ml/cmH$_2$O respectively; there were no significant differences between values for the colonic J pouch and normal rectum (ANOVA).

Recurrence and survival

Local recurrence was seen in seven patients in group 1 and eight in group 2. Distant recurrence was seen in 12 patients in group 1 and four in group 2. There were no patients with distant recurrence only in group 2. There were 52 disease-free survivors in group 1, 14 in group 2 and 39 in group 3. The cumulative rate of local recurrence after CAA is shown in *Fig. 1*. The actuarial probability of local recurrence at 5 years was 11 per cent in group 1, 38 per cent in group 2 and 21 per cent in group 3. There was a significant difference between group 1 and 2 in overall local failures. The median time to local recurrence was 11 (range 6–39) months. The cumulative survival rate in each group is shown in *Fig. 2*. Eighteen patients have died from rectal cancer, 15 with distant metastasis and three with local recurrence. The actuarial probabilities of surviving cancer for 5 years were 73 per cent in group 1, 64 per cent in group 2 and 63 per cent in group 3.

Survival of the colonic J *pouch*

Primary CAA failed in 16 of 100 patients, and reconstruction was undertaken in two patients. Causes of colonic pouch failure are listed in *Table 4*. Nine patients with local recurrence had a permanent stoma at 18 (range 4–38) months after operation. Of six patients with a complication-related failure, three with perianal skin ulcer underwent APE. One patient with a rectovaginal fistula and one with colon cast had successful reconstruction with a colonic J pouch. Seven of the nine patients with local recurrence had APE. One patient refused to have a diverting stoma closed. *Fig. 3* shows the cumulative survival rate of patients who received a colonic J pouch. The proportion of patients surviving with a J pouch at 5 years was 84 per cent. The actual rate of restoration by CAA was 86 per cent at 5 years after the initial operation.

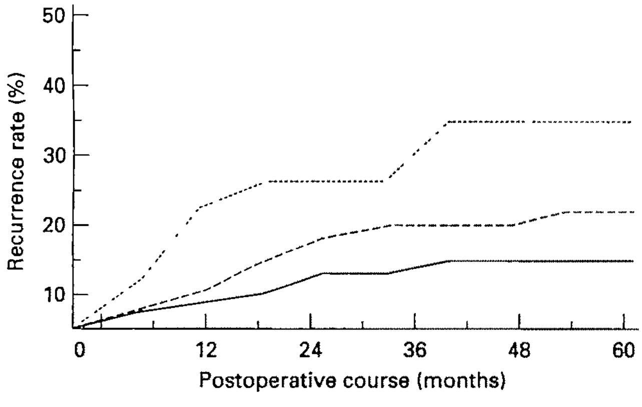

Fig. 1 Local recurrence after anoabdominal rectal resection and colonic J pouch–anal anastomosis with (—, group 1; $n = 68$) or without (····, group 2; $n = 23$) preoperative intraluminal brachytherapy, or after abdominoperineal excision (– – –, group 3; $n = 59$). $P = 0{\cdot}004$ (group 1 *versus* group 2); $P = 0{\cdot}052$ (group 2 *versus* group 3); $P = 0{\cdot}13$ (group 1 *versus* group 3) (generalized Wilcoxon test)

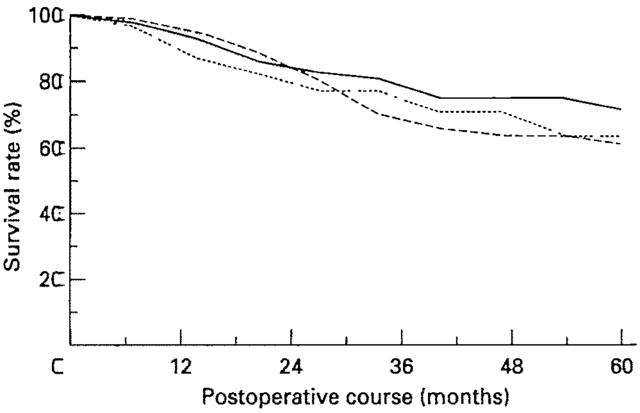

Fig. 2 Survival after anoabdominal rectal resection and colonic J pouch–anal anastomosis with (—, group 1; $n = 68$) or without (··, group 2; $n = 23$) preoperative intraluminal brachytherapy, or after abdominoperineal excision (– – –, group 3, $n = 59$). There were no significant differences between groups (generalized Wilcoxon test)

Table 4 Cause of colonic pouch failure

	Local recurrence	Complication	Patient factor	Total
Unclosed diverting stoma	1	1	1	3
Reconstructed diverting stoma	1	0	0	1
Conversion to permanent stoma	7	3	0	10
Reconstruction of coloanal anastomosis	0	2	0	2

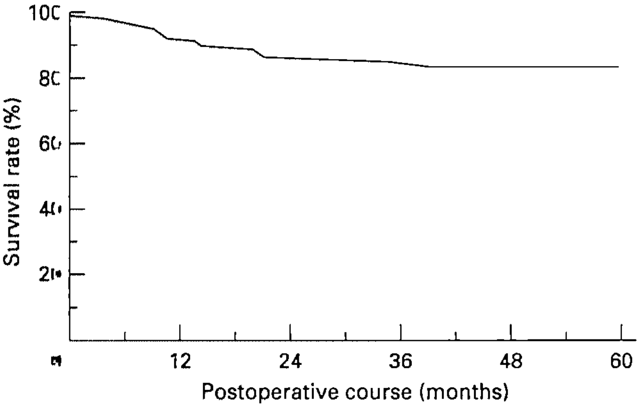

Fig. 3 Survival of 100 patients who underwent anoabdominal rectal resection and colonic J pouch–anal anastomosis

Discussion

More than 20 years have passed since coloanal anastomosis was introduced. Early reports of coloanal anastomosis concentrated on the functional outcome of the operation. Urgency, soiling and highly frequent stooling continued to cause problems after straight coloanal anastomosis[7,11]. Construction of the J pouch has improved these results. The maximum tolerable volume of the J pouch ranges from 200 to 335 ml[10–15]. Decreased anal canal pressures recovered to over 60 per cent (of normal values) at 6 months, and to over 80 per cent at 12 months after operation[11]. Both a preserved anal sphincter and a constructed pelvic reservoir should be considered essential elements of CAA.

Preoperative IBT of 80 Gy affected the decreased anal canal tone and J pouch volume, with frequent defaecation and soiling. A moderate dose of 30 Gy may be more suitable before CAA[20]. In this study, it was realized that incomplete evacuation was the most frequent symptom after CAA. A need for laxatives and evacuation difficulty also correlated with incomplete evacuation. If the J pouch is too large or has an elongated apical pouch bridge, there will be retention. Patients in group 1 had a higher incidence of postoperative complications than those in group 2, indicating that IBT increased the incidence of septic small bowel and perianal skin complications. However, the incidence of severe complications that required surgical intervention was significantly higher in patients with high-dose IBT (40–80 Gy) than in those who had moderate-dose therapy (30–40 Gy). Moderate-dose IBT is thus a more suitable adjuvant therapy to decrease the severity and incidence of complications after CAA.

The operative procedure affects the rate of local recurrence, which ranges from 10 to 40 per cent[21,22]. Sharp dissection along the pelvis side walls and complete excision of the mesorectum are important for complete resection[21,23]. There was no significant difference between the local control rate for APE and that for CAA alone. Postoperative and oncological results after sphincter-saving operations and APE are comparable for tumours with similar features[21,22]. Most of the lesions in this series were located less than 6 cm from the anal verge, representing tumours which are classically treated by APE. The difference in local control rates between group 1 and group 2 suggests that IBT might decrease the rate of local recurrence. There was no statistically significant difference in tumour shrinkage provided by IBT doses over 30 Gy[16]. IBT of 30 Gy also provides superior functional results[20]. The authors now routinely provide a total IBT dose of 30 Gy, and calculate a time–dose factor of less than 250[16,24].

Sixteen of 100 J pouches failed. Local recurrence and IBT-related complications were the major cause of pouch breakdown. However, two of the six J pouches with complications were reconstructed. One patient's complication was not due to CAA itself but resulted from psychological problems. Intestinal continuity was retained for 86 per cent of patients at 5 years after operation.

This experience supports the use of CAA in patients with low rectal carcinoma. Preservation of anal structure by a transanal approach and colonic J pouch provided good functional results. Preoperative IBT may contribute to better oncological results. This treatment option resulted in over 80 per cent of the patients in this series avoiding a permanent stoma.

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Incidence of hereditary non-polyposis colorectal cancer in a population-based study of 1137 consecutive cases of colorectal cancer

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Background Previous reports have indicated that 5–13 per cent of colorectal cancer is hereditary. However, the proportion of cases arising as a result of mutations in the hereditary non-polyposis colorectal cancer (HNPCC) genes remains to be determined.

Methods This study is a part prospective, part retrospective review of all cases of colorectal cancer from a district hospital over 14 years. Some 1137 consecutive patients with colorectal cancer were questioned about their family history of cancer and details were logged on a database. For the past 4 years each case has been re-evaluated where possible.

Results Some 118 patients indicated initially that they had a first-degree relative with colorectal cancer, but on re-evaluation there were significant discrepancies. Only three cases (0·3 per cent) occurred in families which strictly fulfilled the criteria for HNPCC and there were no cases of familial adenomatous polyposis. A total of 16 patients (1·4 per cent) fulfilled looser criteria for HNPCC.

Conclusion This population-based study has shown a lower frequency of familial bowel cancer than previous studies and may reflect a lower incidence of inherited mutations in the HNPCC DNA mismatch repair genes than is currently accepted.

Several of the genes responsible for colorectal cancer have been identified, localized and cloned[1]. Attention has focused on the clinically distinct familial adenomatous polyposis (FAP), leading to the cloning of the FAP gene on chromosome 5 in 1991[2]. FAP is rare, but between 5 and 8 per cent of all colorectal cancer is inherited[1,3]. Other hereditary forms of colorectal cancer include hereditary non-polyposis colorectal cancer (HNPCC) types I and II. There is now evidence of an increased risk of colorectal cancer with *BRCA1* gene mutations[4]. Four genes have recently been cloned which account for the majority of families with HNPCC[5–8]. While replication error (RER) abnormalities can be found in about 13 per cent of all colorectal cancers[9] and are nearly always present in HNPCC[10], recent studies suggest that they are not a particular feature of non-HNPCC familial aggregation[11]. This study was designed to determine the proportion of colorectal cancer which could be classified as hereditary on the basis of family history in a population-based study of 1137 consecutive patients.

Patients and methods

Patients who presented to Trafford General Hospital, Manchester (service population 215 000), since May 1981 with a colorectal cancer have been questioned about a family history. This extended to all cases of colorectal cancer in first- or second-degree relatives, but included a family history of other cancers. From May 1991 patients who previously reported a family history of colorectal cancer have been recalled to the clinic. If they had died a questionnaire was sent to relatives. In addition, a detailed questionnaire was sent to all new patients with colorectal cancer (or their relatives if deceased) who presented after January 1990, and to surviving individuals presenting before 1990. The questionnaire recorded names, addresses and dates of birth of all first-degree relatives, and any second-degree relatives who had developed cancer. It also asked for dietary information and history of other bowel disorders Ages of relatives both alive and dead as well as cause of death were ascertained.

All new patients with colorectal cancer since January 1992 were interviewed prospectively. A detailed family tree of first- and second-degree relatives was drawn from interview and questionnaire data. All cases of cancer were verified by reference to hospital notes, cancer registry data or death certificate. The family trees were classified for HNPCC according to Amsterdam criteria (*Table 1*)[12], or by looser criteria used previously[13]. Groups of patients presenting before and after 1990 were analysed separately.

Table 1 The Amsterdam criteria for diagnosis of hereditary non-polyposis colorectal cancer

Amsterdam criteria[12]
At least three relatives should have histologically verified colorectal cancer; one of them should be a first-degree relative of the other two. Familial adenomatous polyposis should be excluded

At least two successive generations should be affected

One of the relatives should be below 50 years of age when the colorectal cancer is diagnosed

Additional (looser) criteria[13]
Three cases of colorectal cancer at any age
Endometrial, ovarian, ureteric or other gastrointestinal tract cancer substituted for colorectal cancer

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Results

Patients before 1990

After correction for initial inaccuracy of history 70 of 663 patients had information to indicate a first-degree relative with bowel cancer (*Table 2*).

Patients since 1990

Questionnaires sent a minimum of 1 month after presentation were available from 326 of 474 patients (69 per cent). Some 54 patients indicated a specific first-degree relative with bowel cancer and 40 gave sufficient information to allow an attempt at confirmation of the diagnosis. In 27 of 40 the diagnosis was confirmed from hospital notes, cancer registry data or death certificates. Of the remaining 13 individuals, three had an affected second-degree relative, but no first-degree relative confirmed. In ten cases the diagnosis of colorectal cancer was incorrect; in six another cancer was confirmed and in four bowel surgery had been performed for other reasons. In 15 of 286 patients (5 per cent) who did not initially report a family history, colorectal cancer was identified (false negative) in a relative using data from the questionnaires. Two patients indicated that relatives had been diagnosed since their own surgery, four had corrected the initial negative information, two had been unable to give a history at presentation and the remaining seven had reported another cancer in their family which was subsequently found to be colorectal in origin. Therefore, 11 patients had given a true false-negative history at presentation.

In total 56 of 474 patients (12 per cent) had an indication for a positive family history of colorectal cancer of which 42 (75 per cent) were confirmed.

Table 2 Verification of family history

	Family history at presentation		
Confirmation	Positive	Negative	Total
Before 1990 (663 patients)			
No family history (not verified)	0	555	555
No family history of bowel cancer verified	4	34	38
Family history of bowel cancer verified	12	10	22
Family history of bowel cancer not verified	48	0	48
Subtotal	64	599	663
After 1990 (474 patients)			
No family history (not verified)	0	134	134
No family history of bowel cancer verified	13	271	284
Family history of bowel cancer verified	27	15*	42
Family history of bowel cancer not verified	14	0	14
Subtotal	54	420	474
Total	118	1019	1137

*Two individuals who did not profess to a family history of bowel cancer had a relative who suffered from the condition after their own presentation

Full study

Including both the prospective and retrospective arms of the study a family history of colorectal cancer in first-degree relatives was present in 126 of 1137 patients (11 per cent). Detailed pedigrees have been constructed for 94. Only three of 1137 (two before 1990) had a family history consistent with the Amsterdam criteria for HNPCC (*Fig. 1*) and there were no cases of FAP. However, 16 patients (eight before 1990) had at least two first-degree relatives with colorectal cancer and three were only just ineligible (*Fig. 2*). In a further 22 cases there was at least one affected first-degree relative where the index case or relative was diagnosed before 55 years of age.

Twenty-four patients were less than 45 years old when colorectal cancer was diagnosed; four had an affected first-degree relative (including patients in two of the three families with HNPCC). A further 66 patients were diagnosed between 45 and 54 years of age, of whom eight (12 per cent) had an affected first-degree relative (including patients in one of the three families with HNPCC). A further probable patient with HNPCC presented aged 67 years with caecal cancer, but had previously developed rectal cancer at the age of 46 years and endometrial cancer at the age of 52 years; both her father and sister were registered as having gastrointestinal carcinoma.

No additional families with HNPCC were identified, even allowing for other HNPCC-type tumours (endometrium, ovary, stomach, urinary tract substituted for colorectal cancer). Some 138 (12 per cent) of 1137 patients with colorectal cancer subsequently developed another primary cancer or reported a previous primary cancer. Eight had three primaries and three had four. Seventeen patients (12 per cent) have had at least two HNPCC primaries where one occurred at age 60 years or under and 11 had developed breast cancer under the age of 60 years before the onset of colorectal cancer (*Table 3*).

Discussion

This study has revealed a very low frequency (0·3 per cent) of HNPCC, by the Amsterdam criteria. Allowing a more inclusive set of criteria (*Table 1*) the rate was only 1·6 per cent. Previous studies have reported an incidence of 1·0–5·5 per cent[14–19], often using looser criteria. Only two previous reports are as large as this series[15,16]. The most recent study by Mecklin[17], which used strict criteria for HNPCC, found an incidence of only 1 per cent. The

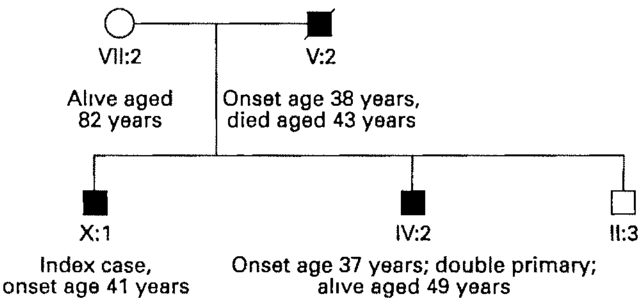
VII:2
Alive aged 82 years
V:2
Onset age 38 years, died aged 43 years
X:1
IV:2
II:3
Index case, onset age 41 years
Onset age 37 years; double primary; alive aged 49 years

Fig. 1 Example of a family with hereditary non-polyposis colorectal cancer fulfilling the Amsterdam criteria. The index case presented aged 41 years; both father and brother also developed colorectal cancer

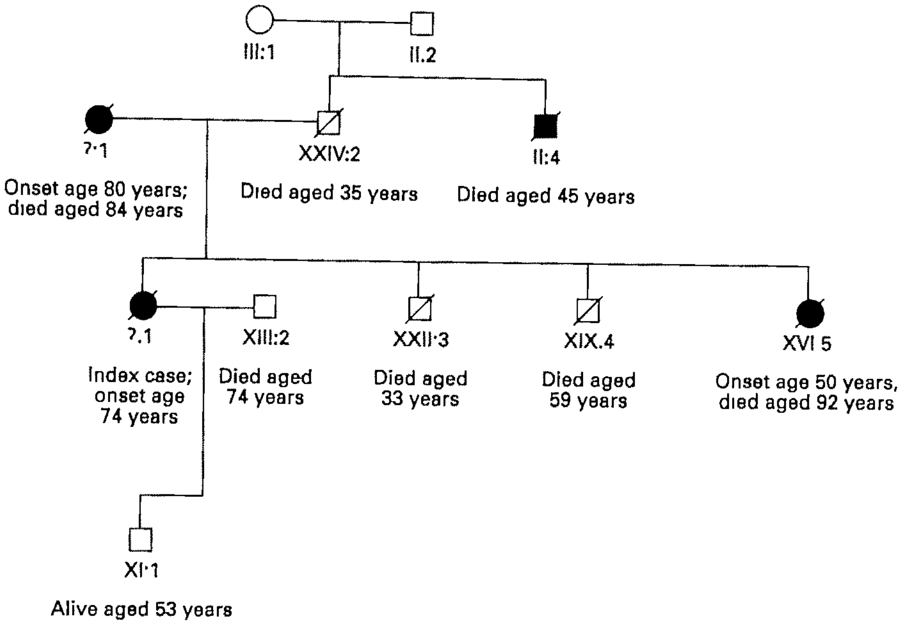

Fig. 2 Example of a family which misses classification using the Amsterdam criteria. The index case presented aged 74 years; the sister, mother and paternal uncle developed colorectal cancer aged 50, 80 and 45 years respectively The family does not fulfill the criteria for hereditary non-polyposis colorectal cancer, but the early death of the father may implicate the paternal side of the family, although the old age of the index case may mean that she is a phenocopy even if the disease is hereditary

Table 3 Double primary cancers occurring in the Trafford colorectal cancer series, where at least one primary occurred in a patient aged 60 years or under

	Other primary		
Age of patient at presentation with colorectal cancer (years)	Location	Age at presentation (years)	Family history of colorectal cancer
Patients with a second HNPCC tumour			
54	Endometrium	52	No
67	Endometrium	52	Yes
	Rectum	46	Yes
48	Colon	50	No
66	Colon	53	No
64	Endometrium	50	No
60	Ovary	60	No
59	Stomach	62	No
79	Colon	53	No
58	Bladder	56	No
60	Colon	61	Father (68)
67	Bladder	60	Father (87)
58	Ovary	59	No
70	Bladder	56	No
70	Stomach	59*	No
66	Endometrium	52	No
74	Rectum	49	No
58	Colon	58	No
Patients with breast cancer			
53	Breast	47	No
65	Breast	45	No
71	Breast	49	No
61	Breast	41	No
70	Breast	60	No
61	Breast	53	No
66	Breast	51	No
61	Breast	53 (Left)	No
	Breast	56 (Right)	
56	Breast	56	Father (70)
72	Breast	42	No
70	Breast	40*	No

Values in parentheses are age at presentation. *One patient who had both stomach and breast primaries HNPCC, hereditary non-polyposis colorectal cancer present study was partly retrospective and significant family histories could have been missed. None the less the incidence of family history was similar in both parts of the study, and two of the three patients with HNPCC were identified in the retrospective part. There were as many false positives as false negatives even in the prospective data.

Although the Amsterdam criteria are useful to facilitate DNA linkage and mutation analysis, they do none the less provide criteria which on the whole exclude chance aggregations of colorectal cancer. Laborious search of the four mismatch repair genes in which causative mutations have been found (*hMSH2, hMLH1, PMS1, PMS2*) is likely to identify a mutation in around 70 per cent of cases[20]. However, non-HNPCC aggregations are unlikely to have an HNPCC mutation[10]. Reports which estimate that 13 per cent of colorectal cancer may be due to inherited mutations in the mismatch repair genes are probably exaggerated. The microsatellite instability seen in 13 per cent of sporadic colorectal tumours[21] is probably due to somatic mutations in the mismatch repair genes rather than mutations in the germline. A more conservative estimate for the involvement of the HNPCC genes would be less than 5 per cent.

Some of the discrepancies between the reported frequencies of HNPCC could also be due to geographical variation. One local family with HNPCC could have contributed four or five colorectal cancers in the timescale of the present study. It is therefore important to take the average of a number of large population-based studies when determining the frequency of HNPCC, ensuring that the same criteria are used for each study.

This study has also highlighted the inaccuracy of family history if a non-inquisitorial approach is taken. While this appears to be more of a problem with older patients, significant inaccuracies are often uncovered in the young. This may mean that screening is not offered to individuals at high risk, or that it is offered inappropriately to those at low risk. Kee and Collins[22] found similar discrepancies in their series. Stephenson *et al.*[19] had a high concordance with patients' information in a smaller study, probably as a result of a more inquisitorial approach as families were visited at home.

The majority of HNPCC and other high-risk families occur in the context of index cases whose diagnosis was made under 55 years old. It should be routine practice to obtain a detailed family history from such patients. If this is verified positive for an HNPCC lesion, family screening should be offered[23,24]. In this study screening would have been offered to only 39 of the 1137 index cases' families. If all patients diagnosed under 45 years and all cases where there were at least two first-degree relatives affected were included this increases to 146 of 1137. This would increase still further if relatives of patients with two primary lesions were screened. The five patients with endometrial cancer should be considered high risk as this is the second commonest tumour in HNPCC[5].

This study demonstrated a low incidence of families with highly penetrant, dominantly inherited colorectal cancer in an unbiased population-based sample of 1137 consecutive patients with colorectal cancer. Fewer families require screening than previously thought. The HNPCC genes may be of less value in targeting screening unless they are involved in less penetrant forms of hereditary colorectal cancer. Family histories are often inaccurate and a more inquisitorial approach is required especially in patients under 55 years old.

Acknowledgements

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Electrically stimulated smooth muscle neosphincter

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Background Most patients undergoing total anorectal reconstruction suffer some degree of incontinence despite the incorporation of an electrically stimulated gracilis neosphincter. As smooth muscle has the ability to maintain prolonged contraction without fatigue, the aim of this study was to assess the feasibility of developing an electrically stimulated smooth muscle neosphincter.

Methods Electrical stimulation of the rabbit colon was performed via intramural wire electrodes using a constant voltage DC stimulator. Contractile activity was recorded by serosal strain gauges and an intraluminal pressure probe.

Results Basal colonic pressure was 4–13 (median 11) cmH_2O. Peak pressures generated by stimulated contractions (10 V, 1 ms, 10 Hz) ranged from 14 to 37 (median 26, $n = 36$) cmH_2O and were significantly higher than those with spontaneous contractions ($P = 0{\cdot}005$). During continuous stimulation contractions lasted for 45–96 (median 74) s. Intermittent stimulation using trains of electrical pulses of 1–2-min duration at 1–2-min intervals produced repeated contractions. Alternative contractions were produced when intermittent electrical stimulation was performed at two sites alternately with two pairs of electrodes more than 2·5 cm apart, producing a sustained high-pressure zone.

Conclusion An electrically stimulated smooth muscle neosphincter is feasible. It has potential applications in the management of faecal incontinence.

Anal sphincter reconstruction plays a crucial role in the management of faecal incontinence resulting from irreparable anal sphincter defects. The only other treatment option in these patients is a permanent stoma which is associated with considerable physical and psychological morbidity[1].

Previous attempts at anal sphincter reconstruction have involved the use of a nearby skeletal muscle[2–9], the most successful being electrical stimulation of the transposed gracilis muscle[10,11]. The electrically stimulated gracilis neosphincter (ESGN) also forms a component of total anorectal reconstruction following rectal excision[12,13]. Although the ESGN provides good results when used in patients with faecal incontinence due to a defective anal sphincter, most of the patients who have undergone total anorectal reconstruction suffer from some degree of incontinence[1,14].

Most sphincters in the body are fully or partly composed of smooth muscle. The smooth muscle component of the anal sphincter complex, the internal anal sphincter, is mainly responsible for the resting anal tone[15] and it plays an important role in the maintenance of continence as suggested by several manometric, electromyographic, ultrastructural and pharmacological studies showing abnormalities of the internal anal sphincter associated with incontinence[16]. Smooth muscle, because of its natural physiological properties, offers a functionally advantageous alternative to skeletal muscle in sphincter reconstruction: it provides prolonged tonic contraction with little fatigue, can generate an amount of force equal to that of skeletal muscle per unit cross-sectional area and has an ability to shorten to a far greater percentage of its initial length while maintaining almost full force of contraction.

In an attempt to design an adequate replacement for the internal sphincter component of the anal sphincter, the feasibility of developing an electrically stimulated smooth muscle neosphincter, which could be used either alone or as an adjunct to the ESGN, was explored. To achieve this, initially the electrical parameters required to produce contraction in colonic smooth muscle were established.

Materials and methods

Experiments were performed on 25 New Zealand White rabbits anaesthetized with 25 per cent urethane. The experimental procedure was approved by the Home Office, London, and complies with The Animal (Scientific Procedures) Act 1986. At laparotomy, a pressure probe (Gaeltec, Isle of Skye, UK) was introduced into the lumen of the colon 5 cm distal to the caecum through a small colotomy to record intraluminal pressure at the site of electrical stimulation. A serosal strain gauge (RB Products, Madison, Wisconsin, USA) was sutured in circumferential orientation to detect the radial force of contraction. Strain gauge activity was amplified and recorded on a chart recorder (*Fig. 1*). Double-armed polymer-coated multifilament stainless steel wire electrodes (0 Flexon; American Cyanamid Company, Wayme, New Jersey, USA) were used as stimulating electrodes The non-insulated end of the wire was anchored into the colonic muscle layer with the help of the needle attached to it.

Electrical stimulation was performed using a constant voltage DC stimulator (Grass SD9, Grass Medical Instruments, Quincy, Massachusetts, USA). The equivalent current was calculated by measuring the potential difference across a small resistance (10 Ohm) connected in series with the rabbit colon, using a cathode ray oscilloscope.

In the initial eight experiments the electrical parameters required to produce contraction were established. A basal

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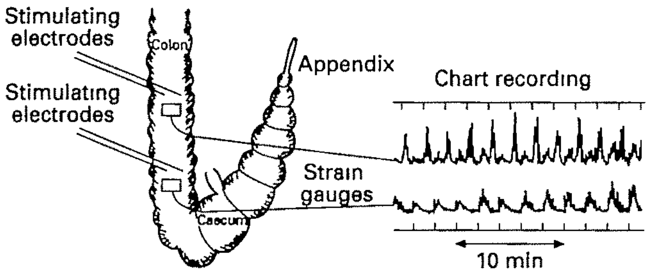

Fig. 1 Electrically stimulated smooth muscle neosphincter. Strain gauge activity during alternate electrical stimulation of the rabbit colon with two pairs of electrodes 4 cm apart is shown. The vertical bars at the top and bottom of the trace represent stimulation of the distal and proximal sites with 10-V, 1-ms pulses at 10 Hz

recording was performed for 30 min or until cessation of the initial spontaneous contractions. Electrical stimulation with square wave biphasic pulses was performed with voltage 10, 12 and 14 V; pulse duration 0·5, 1, 2, 5, 10, 20 and 50 ms, and frequency 2, 4, 6, 8 and 10 Hz.

Direct smooth muscle stimulation was performed via one and then two pairs of intramural electrodes. The distance between the two pairs of electrodes was varied and the effect of alternate stimulation was studied by recording the contractile activity of the colon with two serosal strain gauges implanted at both sites of stimulation.

Electrical stimulation was initially performed on intact colon. Later, the colon was divided at two places leaving the mesentery intact, and stimulation of an isolated segment measuring 5 cm in length was performed.

The colon was inspected for macroscopic evidence of damage at the electrode implant sites. Viability of the stimulated segment of bowel was tested by mechanical and electrical stimulation.

Statistical analysis

Non-parametric tests were used for statistical analysis. The peak pressures produced by spontaneous and electrically stimulated contractions were compared using the Mann–Whitney *U* test. The Kruskal–Wallis test for multiple comparisons was used to assess the effect of varying voltage, frequency and pulse duration on intraluminal pressure.

Results

Basal colonic pressure was 4–13 (median 11) cmH_2O ($n = 25$). Spontaneous contractions occurred at the rate of 3–4 per 10 min with peak pressures of 9–25 (median 17) cmH_2O ($n = 28$). The spontaneous contractions ceased to occur after 20–30 min. With 1-ms pulses at 10 Hz, stimulated contractions occurred at the threshold of 10 V (equivalent current 8 mA) consistently. The latency of contraction ranged from 12 to 18 (median 16) s. Individual contractions lasted for 45–96 (median 74) s even when the electrical stimulus was applied for up to 300 s. Peak pressures were achieved in 24–80 (median 40) s. Peak pressures generated with stimulated contractions at 10 V, 1 ms at 10 Hz were 14–37 (median 26) cmH_2O ($n = 36$) and were significantly higher than those with spontaneous contractions ($P = 0·005$).

With 1-ms pulses at 10 Hz, increasing the voltage from 10 to 14 V produced a statistically significant increase in the intraluminal peak pressure ($n = 8$, $P = 0·01$) (*Fig. 2a*).

When stimulation was performed with 10 V at 6 Hz, increasing the pulse duration from 0·5 to 50 ms produced an increase in the intraluminal pressure ($n = 6$, $P = 0·01$)

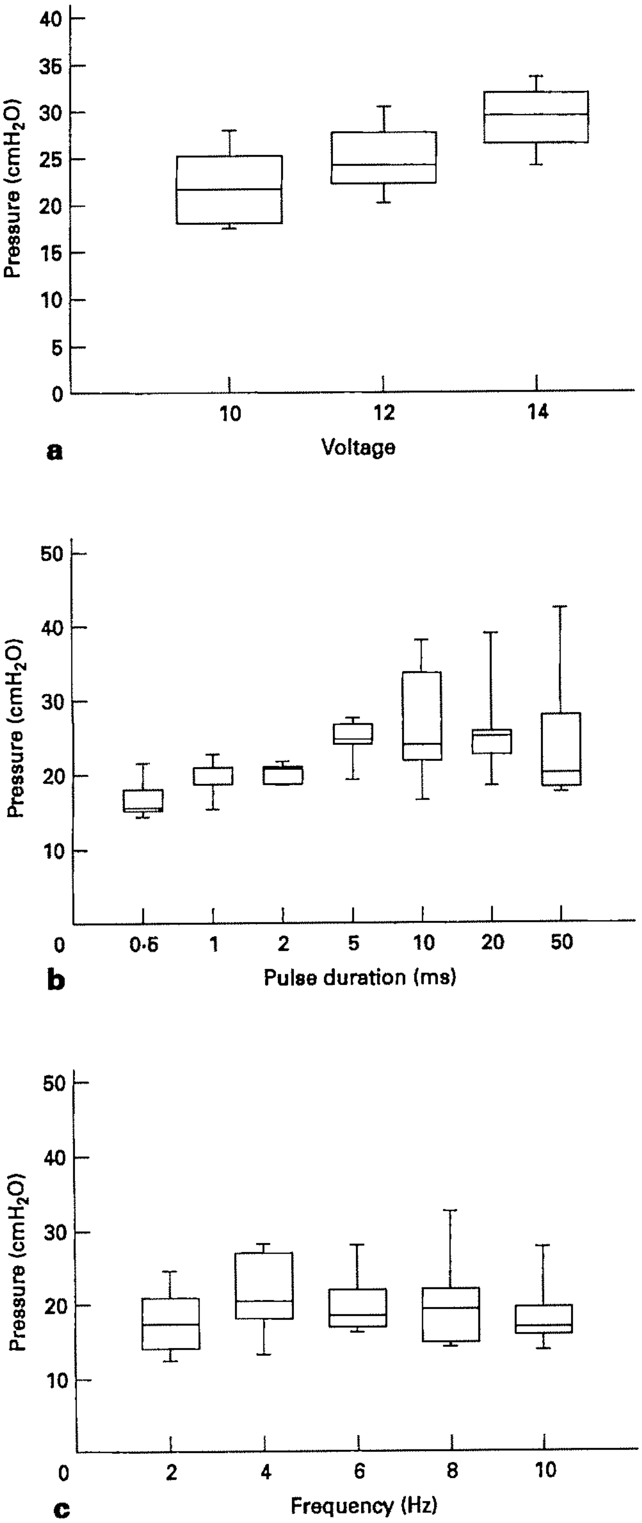

Fig. 2 Effect of increasing a voltage, b pulse duration and c frequency on colonic intraluminal pressure. Stimulation was performed a at 10 Hz using 1-ms pulses; b with 10 V at 6 Hz; c using 10-V 1-ms pulses. Boxes are median (interquartile range) and vertical bars are the 10th–90th percentile. a $P = 0·01$ ($n = 8$); b $P = 0·01$ ($n = 6$); c $P = 0·53$ ($n = 10$) (Kruskal–Wallis test for multiple comparisons)

(*Fig. 2b*). However, with a pulse duration of more than 1 ms, bubbling occurred at the site of the electrodes. At a pulse duration of 50 ms the frequency of stimulation could not exceed 6 Hz.

Increasing the frequency from 2 to 10 Hz had no significant effect on the intraluminal pressure when stimulation was performed using 10-V, 1-ms pulses ($n = 10$, $P = 0{\cdot}53$) (*Fig. 2c*).

Intermittent stimulation with trains of pulses of 1–2-min duration at 1–2-min intervals (individual pulses of 10 V, 1 ms, 10 Hz) produced repeated contractions throughout the experiments which lasted for 6 h. Intermittent stimulation at two sites alternately with two electrode pairs more than 2·5 cm apart produced repeated contractions at both sites alternately (*Fig. 1*). Further reduction of the distance between the electrode pairs produced a single band of contraction which failed to respond to alternate stimulation. Isolated segments of 5 cm in length produced by transection of the colon at two sites continued to respond to electrical stimulation producing intraluminal pressures similar to those of intact colon.

There was no evidence of damage at the site of stimulation on macroscopic examination. The colon remained viable as evident from its appearance and from continued contractile responses to electrical and mechanical stimulation at the end of experiments lasting about 6 h.

Discussion

This study reports the development of a dynamic sphincter mechanism by intramural electrical stimulation of colonic smooth muscle. To achieve a sphincteric effect it is necessary to have a localized zone of high pressure. This was achieved by intermittent stimulation of two adjacent segments alternately as contraction of any given segment could not be sustained with a prolonged stimulus. This was not due to fatigue of the colonic muscle because intermittent stimulation produced repeated contractions of similar magnitude at the same site for 6 h. Alternate stimulation of adjacent segments of bowel was performed with two pairs of electrodes to produce contraction at one site during the latent and relaxation periods at the other site with a minimum interelectrode distance of 2·5 cm. Further reduction of the distance between the electrode pairs produced a single band of contraction which could not be sustained.

As the peak pressures generated by stimulated contractions were significantly higher than those during spontaneous contractions, a pressure gradient could be maintained at the site of electrical stimulation even in the presence of spontaneous contractions occurring proximally.

Following the initial description of a smooth muscle sphincteroplasty[17] for the development of continent abdominal colostomy in 1982, several sphincteroplasties have been attempted to develop continence in perineal colostomies[18–22]. These procedures involve wrapping a seromuscular cuff around the colon. Although some success was claimed for such a sphincter, particularly in developing an abdominal colostomy, widespread scepticism has prevented its adoption in clinical practice. Adynamic narrowing at the site of the sphincter, resulting from scarring, possibly provides a mechanical hindrance to the passage of luminal contents.

Electrical stimulation has been extensively used as a method to elicit contraction in strips of gut musculature *in vitro*. Direct smooth muscle stimulation has also been performed to improve emptying of ileal[23] and colonic[24] pouches in animals. A wide spectrum of electrical parameters is used in such preparations, and it would be misleading to extrapolate these parameters to humans. There have been no studies on electrical parameters required to induce colonic contraction by direct electrical stimulation in humans.

At short pulse durations, the response to electrical stimulation is likely to occur as a result of nerve stimulation. However, the voltages required to obtain a contractile response in the present experiments are higher and the latent period is longer than that expected of a neuromuscular response. This may be because of the diffuse innervation and possible neurohumoral mechanisms involved in the excitation of gut musculature. The localized contractions occurring circumferentially following intermittent electrical stimulation may be due to the syncytial property of circular muscle as the electrical slow waves occur in phase around the circumference of the bowel and are out of phase in the longitudinal axis of the bowel[25]. Although the effect on peristaltic activity was not studied in these experiments, it is likely that, once produced, a stimulated contraction would travel in both directions along the intact bowel, particularly in the colon where contractions are seen to go backwards and forwards while mixing takes place. Retroperistaltic activity may be beneficial in preventing emptying.

The isolated segment of colon continued to respond to electrical stimulation producing pressures similar to those of intact colon. An isolated segment interposed in a retroperistaltic fashion at an abdominal or perineal stoma may provide an additional safeguard towards the maintenance of continence.

In conclusion, a sphincteric effect can be achieved in the rabbit colon by intermittent electrical stimulation repeated alternately at two sites. An electrically stimulated smooth muscle neosphincter has possible applications for the treatment of faecal incontinence and in total anorectal reconstruction where it could be used either alone or as an adjunct to the ESGN. It also has potential application in the development of continent stomas.

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New suturing device for transanal endoscopic microsurgery

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Transanal endoscopic microsurgery (TEM) was first developed by Buess *et al.*[1] in 1983; it is a minimally invasive surgical technique for the treatment of large sessile polyps and early rectal cancer. One specific problem is that the suturing technique must be performed in the limited space of a rectoscope measuring 4 cm in diameter and this is generally difficult. Such suturing is often time consuming, even when using instruments specially designed for TEM. An innovative instrument, the Endo Stitch (AutoSuture, Norwalk, Connecticut, USA), is described, which facilitates the successful performance of endoscopic suturing during TEM.

Surgical technique

The Endo Stitch measures 10 mm in diameter. A needle is used and the suture is secured to its centre; the needle is pointed at both ends, allowing it to pass through tissue in both directions. The Endo Stitch may be used to close a defect with a transverse continuous suture after removing the specimen. *Fig. 1a* shows the needle held on one side of the instrument The closing action of the handle passes the needle through the tissue from one side of the instrument to the other, at which point the needle is transferred and locked into the opposite needle holder by rotating the toggle lever (*Fig. 1b*). After the needle has been passed in this fashion, the stitch is pulled through the tissue (*Fig. 1c*). At this point the needle is automatically ready for the next stitch. Continuous suturing is accomplished by repeating the above manoeuvre, and silver clips act as a substitute for knots.

From June 1995 to August 1996, the Endo Stitch was used for TEM in 11 patients with rectal tumours. The suturing time ranged from 5 to 24 (mean 14) min; no complications were observed.

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Discussion

A conventional needle holder is often difficult to use in TEM and suturing significantly increases the operating time; it also takes a long time to perfect the technique. The Endo Stitch, which was developed as a laparoscopic suturing device, eliminates the need for complicated conventional suturing. It is especially useful because it reduces the time needed to perform TEM.

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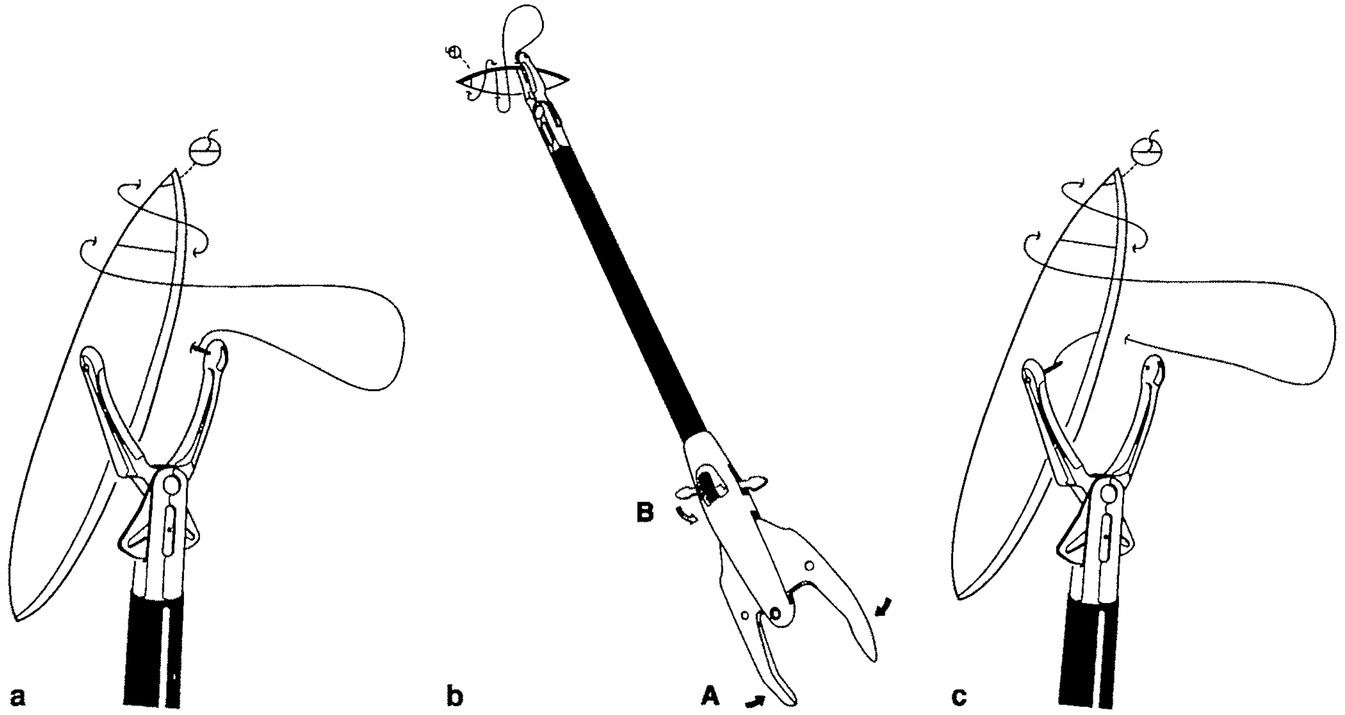

Fig. 1 a Needle held on one side of the Endo Stitch. b The needle is passed through the tissues and to the opposite side of the instrument by closing the handles (A). The needle is transferred and locked into the opposite needle holder of the instrument by rotating the toggle lever (B). c The suture is then pulled through the tissues

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Randomized trial of a biofragmentable bowel anastomosis ring in high-risk colonic resection

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Background Biofragmentable anastomosis ring (BAR) has been proven to be a safe anastomotic device in elective surgery. The use of this anastomotic ring in high-risk patients has not been established.

Methods During a 5-year period (1990–1995), 100 high-risk patients undergoing colonic resection and suitable for a primary anastomosis were allocated randomly to a standard suture technique or to anastomosis performed with a BAR. High risk was defined as large bowel obstruction, complicated diverticular disease, Crohn's disease, local cancer recurrence, previously irradiated colon, and trauma to the colon or rectum. The patients were equally distributed to the two groups regarding sex, age, emergency surgery and concomitant diseases.

Results In three patients allotted to the BAR group, the device could not be used. There were three (6 per cent) postoperative deaths in each group; none was related to anastomotic problems. Three anastomotic dehiscences were diagnosed, two (4 per cent) in the BAR group and one (2 per cent) in the suture group. Postoperative complications and postoperative recovery were similar.

Conclusion This study shows that the BAR anastomosis probably is as safe as the standard hand-sewn anastomosis in high-risk colorectal surgery. As the cost of a BAR anastomosis is substantially higher than that for a hand-sewn anastomosis, the latter technique is still the preferred method in the authors' unit.

The biofragmentable anastomosis ring (BAR), composed of polyglycolic acid and barium sulphate, with the commercial name VALTRAC (Davies and Geck Division, American Cyanamide, Danburry, Connecticut, USA), has been developed to obtain a sutureless bowel anastomosis. This technique was first described by Hardy and colleagues[1] in an experimental study on pigs and the first report of BAR anastomoses in human subjects[2] was presented in 1987. Three large randomized trials on small and large bowel anastomoses have shown that sutureless anastomoses with the BAR are as good as hand-sewn or stapled anastomoses[3–5]. This type of anastomosis has also been compared with a circular stapling device in colorectal anastomoses, with no observed differences in the postoperative course[6]. The feasibility of using the BAR has been shown in several non-randomized studies in colorectal surgery[7–9], as well as in anastomoses of the upper gastrointestinal tract[10], with no obvious adverse effects on postoperative recovery. However, no firm data have as yet shown that the BAR can be used for anastomosis in high-risk patients.

The aim of this study was to explore within a randomized trial the use of the BAR for large bowel anastomoses in a group of high-risk patients. This report records the feasibility, complication rate and short-term survival following BAR anastomosis.

Patients and methods

Patients

Over a 5-year period from September 1990 to May 1995, a total of 100 patients designated as having a high-risk colonic resection were included in a randomized trial in the authors' unit to have the anastomosis performed with a BAR or by hand-sewn anastomosis (suture group). The age and sex distribution, coexistent disease, and whether or not the patients were operated on as an emergency or elective case are given in *Table 1*. There was no difference regarding coexistent disease between the two groups, with 19 patients in the BAR group and 20 in the suture group. All high-risk patients undergoing colonic resection who were suitable for the formation of a primary anastomosis were eligible for the study. High risk was defined as any of the following categories: (1) large bowel obstruction; (2) complicated diverticular disease (e g. colovesical fistula or abscesses); (3) Crohn's colitis or terminal ileitis involving a right-sided hemicolectomy, (4) local recurrence following previous colonic cancer surgery; (5) any large bowel anastomosis in previously irradiated colon or rectum; and (6) traumatic injury of the colon or rectum.

Terminally ill patients with a life expectancy of less than 3 months were excluded. The suitability for entrance in the trial was finally determined at laparotomy before construction of the anastomosis. Randomization was carried out by the opening of a sealed envelope in the operating theatre. Informed consent was obtained from all patients before surgery and the study was approved by the ethics committee, Uppsala University

The diagnoses at surgery are presented in *Table 2*. The surgical procedures performed in the BAR group were sigmoid resection (18 patients), ileocolic resection (19), right-sided hemicolectomy (five), left-sided hemicolectomy (five) and subtotal colectomy (three). The corresponding values in the suture group were 20, 16, seven, one and four, and two transverse colectomies.

Surgical technique

An appropriately sized BAR was used in designated patients. The various sizes used in this study were 28 mm with a gap of 1·5 mm in four cases, 28 mm with a gap of 2·0 mm in seven cases, 31 mm with a gap of 1·5 mm in nine cases, 31 mm with a gap of 2·0 mm in 29 cases, and one unknown. The purse-string suture used in the BAR group was 3–0 or 4–0 polydioxanone (PDSII,

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Ethicon, Norderstedt, Germany). Extra supporting stitches with 3–0 polyglactin (Vicryl; Ethicon) were placed in ten cases. In the suture group the anastomotic technique was according to the practice of the operating surgeon. A single-layer, continuous, seromuscular anastomosis was performed in nine cases using a double-armed 4–0 polydioxanone suture. The other 41 patients had a double-layer anastomosis with a continuous mucosal layer and an interrupted serosa to serosa layer with 3–0 polyglactin.

Bowel preparation, if appropriate, was done according to the authors' usual routine with an oral washout enema Laxabon (Tika, Lund, Sweden) in elective cases and ontable lavage in emergency cases. All patients received perioperative antibiotic prophylaxis. Those having elective surgery received 10 ml Bactrim (Roche, Basel, Switzerland) intravenously 1 h before surgery combined with tinidazole (Fasigyn; Pfizer, New York, USA) 2 g orally the evening before operation. Those operated on as an emergency case received cefuroxime (Zinacef; Glaxo, Greenford, UK) 1·5 g intravenously and metronidazole (Flagyl; Rhone-Poulenc Rorer, Paris, France) 1·5 g intravenously. Postoperative antibiotic treatment was given if indicated by the findings at surgery. Prophylaxis against venous thromboembolism was given routinely, using heparin (Klexane; Rhone-Poulenc Rorer). Postoperative management of intravenous fluids, re-establishment of oral fluid and diet, and antibiotic therapy was according to the usual routines in the authors' unit. The scheduled postoperative follow-up was 6 weeks after surgery, but all hospital files have been reviewed for hospital admissions and outpatient visits for abdominal symptoms. All patients have been followed for a minimum of 1 year.

Postoperative complications

Postoperative mortality was registered as inhospital mortality. All recorded deaths within 30 days occurred in hospital. The definition of a wound infection was drainage of pus from the wound, and anastomotic dehiscence if a leak was detected at laparotomy or with a water-soluble contrast enema. Contrast enemas to look for anastomotic dehiscence were performed only when indicated. Hospital stay was calculated from the day of operation until discharge. Anastomotic stricture was registered if laparotomy was necessary because of bowel obstruction at the anastomosis.

Table 1 Patient details

	BAR ($n = 50$)	Suture ($n = 50$)	*P*
Sex ratio (M:F)	22:28	20:30	0·84*
Mean (range) age (years)	61 (21–92)	57 (14–87)	0·80†
Emergency: elective surgery	24:26	29:21	0·42*
Cardiovascular disease	6	5	
Generalized cancer	5	5	
Diabetes	2	3	
Respiratory failure	1	2	
Sepsis	1	1	
Miscellaneous	4	4	
No coexistent disease	31	30	

BAR, biofragmentable anastomosis ring. *χ^2 test; †Student's *t* test

Table 2 Diagnosis at surgery

	BAR	Suture
Crohn's disease	21	13
Diverticulitis	8 (6)	15 (14)
Colonic cancer	13 (13)	9 (7)
Cancer (other)	3 (2)	2 (1)
Volvulus	2 (2)	4 (4)
Ischaemia	1 (1)	3 (3)
Miscellaneous	2	4
Total	50 (24)	50 (29)

Values in parentheses represent emergency cases. BAR, biofragmentable anastomosis ring

Statistical analysis

Differences between proportions were tested with the χ^2 test, differences between means were tested with Student's *t* test, and differences between medians with the Mann–Whitney *U* test. The results have been analysed according to the principal intention to treat.

Results

Complications at surgery

In total, 50 patients were allocated to have a BAR anastomosis. In three cases the BAR could not be used: in one patient with cystic fibrosis in whom an ileocaecal resection was performed due to mucous obstruction, the distal ileum was extremely thick and enlarged and was impossible to plicate into the BAR; in two other cases the BAR could not be used owing to rupture of the bowel or because the bowel was too narrow. At surgery one patient in the BAR group had an abscess and one had major bleeding. In the suture group one patient had an abscess, one had major spillage, one had major adhesions, and one had small bowel perforation. There was no difference in mean (range) peroperative bleeding between the groups (BAR group 400 (less than 100–16000) ml *versus* suture group 400 (less than 100–4800) ml, $P = 0{\cdot}70$). The mean (range) operating time was similar (BAR group 155 (70–395) min *versus* suture group 150 (80–550) min, $P = 0{\cdot}59$).

Mortality and morbidity

There was no major difference in postoperative complications (*Table 3*). Hospital mortality was similar; three patients died in each group. In the BAR group death was caused by pulmonary embolism, severe bleeding from an ischaemic large bowel, and sepsis and multiorgan failure, and in the suture group it was caused by bleeding from a duodenal ulcer, atherosclerosis in the superior mesenteric artery producing an ischaemic and perforated caecum, and disseminated lung carcinoma. In none of the patients was death related to an anastomotic complication.

Table 3 Postoperative complications

	BAR	Suture
Leakage	2 (1)	1 (1)
Obstruction	3	1 (1)
Bleeding	2 (1) (one died)	1 (1) (one died)
Infection	4 (one died)	6 (2)
Fatigue (cancer)	1	1 (one died)
Pain	2	3
Cardiovascular	2 (1) (one died)	3 (one died)
None	34	34
Total	50 (3) (three died)	50 (5) (three died)

Values in parentheses represent relaparotomies. BAR, biofragmentable anastomosis ring

Table 4 Recovery of bowel function

	Time after operation (days)		
	BAR	Suture	P*
First flatus passed	3 (1–9)	3 (1–18)	0·82
First bowel movement	4 (1–11)	4 (1–21)	0·72
Clear liquids tolerated successfully	5 (3–17)	5 (2–42)	0·81
Full liquids tolerated successfully	6 (3–17)	6 (3–43)	0·92
Low-residue diet tolerated successfully	7 (4–18)	7 (4–43)	0·59
Regular diet tolerated successfully	8 (5–19)	7 (4–43)	0·90

Values are median (range). BAR, biofragmentable anastomosis ring. *Mann–Whitney U test

Relaparotomy was performed in three patients in the BAR group and in five in the suture group. The reasons for relaparotomy were leakage, bleeding and vascular problems (ischaemia of the large bowel) in the BAR group, and leakage, bleeding, obstruction and abscess (two cases) in the suture group. According to *Table 3* there was no overall difference between the two groups regarding postoperative complications, with 34 patients in each group having no complications.

Hospitalization

There was no difference with respect to time from surgery to full tolerance of regular diet by oral intake (*Table 4*). Length of hospitalization was also similar in the two groups (median (range) 9 (6–36) days in the BAR group *versus* 9 (6–45) days in the suture group, $P = 0·7$).

Late complications

All records were examined, and reoperations performed because of anastomotic complications were registered during the follow-up period. Only one relaparotomy for this purpose was performed. This patient, operated on for Crohn's disease, had a BAR anastomosis. Some 6 months later the patient was operated on for an anastomotic stricture. At laparotomy, a short, fibrotic and narrow stricture found at the site of the former anastomosis was resected. Histopathological examination revealed no signs of Crohn's disease, only fibrosis.

Discussion

In this study no increased morbidity or mortality was noticed among patients operated on with the BAR, compared with those having a conventional anastomotic technique. All patients had a high-risk anastomosis according to the study protocol, performed for different colorectal diseases. Although this trial is small, no trend was observed to a difference between the groups. On the other hand, if the BAR were dangerous in this group of patients, a higher trend of adverse effects would have been expected. The authors have calculated that to detect an increase in leak rate from 3 to 5 per cent, 1500 patients would have to be included in each arm assuming a significance level of 0·05 and a power in the test of 90 per cent. However, such a difference is not clinically relevant. From this rather small study it may therefore be concluded that the BAR can be used without any marked increase in adverse effects.

An important aspect in the choice of anastomotic technique is the price. Hand-sewn anastomoses are much cheaper than every other anastomotic technique available. The cost for a hand-sewn continuous seromuscular anastomosis with a double-armed 4–0 polydioxanone suture is approximately one-twentieth that of the BAR anastomosis and one-fortieth to one-fiftieth that of a stapled anastomosis. However, the cost for a BAR is considerably less than that of a stapled anastomosis. The time necessary to complete the anastomosis was not measured in this study. Because the operating time was similar in both groups, the time to create the anastomosis could not differ to any substantial extent between the groups. A possible explanation is that two purse-string sutures have to be placed to construct the BAR anastomosis. The authors have not used the specially designed purse-string device in their unit, but placed the sutures by hand. The time taken to complete an anastomosis with two purse-string sutures in the BAR is then not substantially shorter than that required for an anastomosis made by a single-layer continuous type of suture. Moreover, in three cases it was not possible to use the BAR. This should actually be considered as a failure of the BAR technique, which is not seen when a hand-sewn anastomosis is used.

It has been claimed that the ideal anastomosis should not contain any foreign materials. It must also be simple to construct and safe. The BAR anastomosis does not leave any foreign materials behind. However, this technique involves an approximation of serosa to serosa, inducing secondary healing with an obvious risk of more or less fibrotic healing. There are theoretical reasons to suggest that the best anastomosis would be one in which the bowel layers were only apposed to each other. Thus, the most important part of the healing process is to provide exact coaptation of the mucosal and submucosal layers. Fibrotic stenosis is a well known phenomenon in anastomoses performed with circular staplers where the serosal layers are coapted. However, with the stapling devices such a stricture may be the result of ischaemia due to the staples and/or compression of the bowel ends. Another mechanism may be a stricture due to secondary healing between the serosal layers. Similar strictures have been reported after use of the BAR[11]. In that report, patients who had had a BAR anastomosis after left-sided colonic or rectosigmoid resection in the Finnish randomized trial[7] were followed with sigmoidoscopy and barium enema. One stricture was found among 30 cases, but after extended follow-up there have been three strictures in 400 cases (T. Havia, personal communication). In the present series, one patient has developed a similar stricture.

In summary, this trial has shown that the BAR anastomosis is probably as safe as a standard hand-sewn double- or single-layer anastomosis in high-risk colonic surgery. The cost of the BAR is substantially greater than that of a hand-sewn anastomosis, and therefore hand-sewn anastomoses are used from the ligament of Treitz to the sacral promontory in the authors' unit.

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Ultrasonography and computed tomography reduce unnecessary surgery in abdominal rectus sheath haematoma

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Background Rectus sheath haematoma is a rare cause of abdominal pain. If accurately diagnosed, surgery can be avoided in most cases. This study assessed the role of ultrasonography and computed tomography (CT) in the diagnosis of rectus sheath haematoma.

Methods Thirty cases of rectus sheath haematoma diagnosed over 18 years were reviewed. Mean patient age was 59 years; there were 20 women and ten men. The results of imaging investigations were reviewed to determine their efficiency. Ultrasonography was performed in 21 patients and CT in nine.

Results Arterial hypertension, anticoagulant therapy and strained coughing were the most frequent predisposing factors. The most common clinical manifestation was abdominal pain with a palpable mass. Leucocytosis occurred in 18 patients and the haematocrit fell in 13 patients but markedly in seven. Ultrasonography was diagnostic in 15 of 21 patients imaged, and CT was diagnostic in all nine. Treatment was conservative in 22 patients. Eight patients required surgery: four for diagnosis and four for treatment.

Conclusion Surgery can be avoided in most patients with rectus sheath haematoma. Although the numbers were small, CT appeared to be more accurate than ultrasonography in facilitating the diagnosis.

Rectus sheath haematoma is an accumulation of blood in the sheath of the anterior rectus abdominis muscle, secondary to rupture of an epigastric vessel or muscle tear[1]. It is usually located below the umbilicus where the epigastric vessels are not protected posteriorly by the aponeurotic sheath, although it may occur in the upper abdomen[1,2]. The condition usually occurs in women (sex ratio 2·5 : 1) aged over 50–60 years[3].

The importance of rectus sheath haematoma lies in the difficulty in diagnosis, as clinical, laboratory and radiological data are not very specific. If a diagnosis is established, most cases can be treated conservatively[2,4–6]. The present study is a review of the authors' experience with rectus sheath haematoma; the role of ultrasonography and computed tomography (CT) as diagnostic methods is evaluated.

Patients and methods

Over 18 years, 30 cases of rectus sheath haematoma in 29 patients were recorded. Twenty haematomas were in women and ten in men, and the mean(s.d.) age of patients was 59(13·7) (range 13–81) years. Clinical information on each case was reviewed, together with laboratory data. Abdominal ultrasonography was performed in 21 cases and CT in nine.

Results

In two cases, the rectus sheath haematoma was secondary to injury of an epigastric artery, during inguinal herniorrhaphy in one case and diagnostic laparoscopy in the other. Of the remaining 28 patients, predisposing factors were recognized in 17 (arterial hypertension in 11, anticoagulant therapy in five and essential thrombocytosis in one) and precipitating factors in 18 patients (coughing fits in 13, sudden exertion in three and direct abdominal trauma in two).

Modes of presentation are recorded in *Table 1*. Seventeen rectus sheath haematomas were right-sided: 15 in the right lower quadrant and two in the right hypochondrium. Eleven were located in the left lower quadrant and two were bilateral.

Leucocytosis (white cell count greater than 10 000 cells per mm^3) was recorded in 18 patients. The haematocrit was decreased in 13 patients, although blood transfusion was required in only seven. There was a decrease in platelet count in one case only, and an increased platelet count in the patient with essential thrombocytosis. Coagulation-related parameters were normal in 21 patients and abnormal in nine: five were anticoagulated patients, in all of whom prothrombin activity was less than 18 per cent.

Diagnosis was made on clinical grounds alone in eight cases. Three patients had an early diagnosis (one traumatic, confirmed by puncture, and the two with abdominal wall abscess). In five patients the diagnosis was made late, when a change in skin colour revealed the underlying haematoma. Exploratory tests such as ultrasonography, urography, barium enema or colonoscopy had proved negative. In 15 cases, clinical suspicion was confirmed by ultrasonography and/or CT. In three, the diagnosis was exclusively radiological, following ultrasonography or CT in patients not suspected of rectus sheath haematoma. Finally, the diagnosis was made surgically in four cases: one polytraumatized patient had a decrease in haematocrit and the haematoma was found during exploratory laparotomy; two patients with suspected acute appendicitis; and one with a suspected

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Table 1 Clinical findings and diagnostic procedures in patients with rectus sheath haematoma

	No. of cases	Needle aspiration	Ultrasonography			Computed tomography	Operation
			Total	Positive	Negative		
Painful abdominal mass	17	0	14	11	3	5	2
Painless abdominal mass	7	1	5	3	2	3	0
Abdominal pain, no mass	4	0	2	1	1	1	2
Abdominal wall abscess	2	0	0	0	0	0	0
Total	30	1	21	15	6	9	4

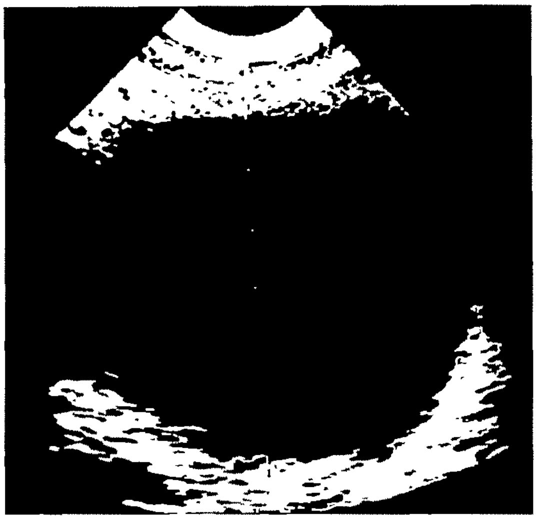

Fig. 1 Ultrasonographic image of rectus sheath haematoma: fusiform sonolucid mass

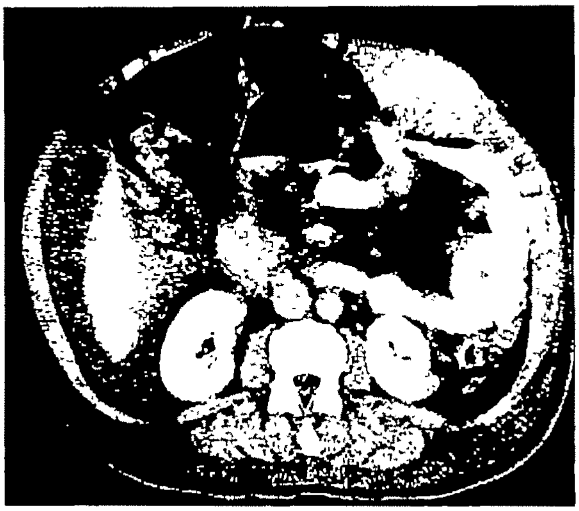

Fig. 2 Computed tomogram of rectus sheath haematoma. Scans at the level of the rectus sheath show haematoma confined to the abdominal wall

incarcerated incisional hernia in a right-sided paramedian scar.

Ultrasonography was performed in 21 cases and was diagnostic in 15; the sensitivity was 71 per cent. Imaging revealed a fusiform longitudinal mass, which was initially sonolucid (*Fig. 1*) but which became increasingly sonodense with organization of the haematoma. In six of these patients the diagnosis was confirmed by CT. Ultrasonography was inconclusive in six cases, of which two were diagnosed by CT; diagnosis in the other four was clinical after complementary examinations ruled out other pathology.

Only nine patients received CT: one as the sole imaging method, six with positive ultrasonography findings to confirm the diagnosis, and two with negative ultrasonography findings. CT was positive in all cases and showed the haematoma confined to the abdominal wall inside the rectus sheath, with a fusiform appearance in cross-sections (*Fig. 2*).

Twenty-two patients had conservative treatment consisting of anti-inflammatory analgesia and discontinuance of anticoagulant therapy.

Eight patients required surgery, four as a diagnostic procedure, proceeding to haematoma evacuation and appendicectomy when appendicitis had been suspected, and in four as a therapeutic manoeuvre. Two patients had evacuation of a steadily growing haematoma and two had an infected haematoma drained and debrided.

Mean hospital stay was 11·6 (range 1–30) days. There were two postoperative complications: one wound infection following appendicectomy and one case of thrombophlebitis. There was no mortality. A single patient developed recurrent rectus sheath haematoma. Appendicitis was suspected at the first admission resulting in surgery, whereas 4 years later recurrent haematoma developed with pain and a palpable mass in the left lower quadrant, and the diagnosis was confirmed by ultrasonography and CT.

Discussion

The most important predisposing factor for rectus sheath haematoma is anticoagulant therapy[2,3,5–8]. The most common precipitating factors are repeated fits of coughing[3]. From a clinical point of view, rectus sheath haematoma symptomatology is non-specific[2,3,5,8] and there are no specific laboratory data[2,4,5,7].

The diagnosis was formerly established by excluding other causes of pain and/or abdominal mass using abdominal radiology, intravenous urography, barium enema, etc.; direct puncture could be diagnostic if doubt persisted[3]. Currently, with the introduction of ultrasonography and CT, a quick and reliable diagnosis can be obtained, ruling out the need for laparotomy[9–11].

In the present study CT was performed in only nine cases, as in the initial years of the study this imaging method was not used routinely. When ultrasonography was conclusive, CT was not generally performed (six of 15 cases).

Treatment for rectus sheath haematoma has traditionally been surgical[3]. There is now a preference for conservative treatment. In the event of a large haematoma with haemodynamic repercussions, or abscess formation, or uncertain diagnosis, surgical treatment is preferable[6,7,12]. Of the eight patients in whom treatment was surgical, only one had preoperative ultrasonography and/or CT. If imaging had been done in the remaining cases, the operation rate would have dropped.

Needle aspiration was used for clinical diagnosis only when there was a change in skin colour, especially before the routine use of ultrasonography and CT. It was not used as a therapeutic method because of the risk of infection, and also because many patients are admitted after several days, which means that the haematoma is organizing.

In conclusion, rectus sheath haematoma is a rare form of false acute abdomen or abdominal mass, and must be taken into consideration by surgeons to rule out unnecessary laparotomy, particularly if pain or a painful mass develops after strenuous activity. Ultrasonography is useful if it is aimed at a site of suspected pathology; however, CT may be the investigation of choice.

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Risk of late perforation in intestinal contusions caused by explosive blast

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Background Despite the predominance of superficial injuries after explosive blast exposure, major morbidity or mortality among immediate survivors is caused by delayed perforation of intestinal mural contusions. Previous studies have suggested that small bowel and colonic contusions larger than 10 mm in diameter are at high risk. This experimental study aimed to identify contusions at high risk of late perforation.

Methods Histological features of injury were classified in 188 blast-induced intestinal contusions in 16 anaesthetized Large White pigs.

Results Some 16 per cent of small bowel and 12 per cent of colonic contusions were at high risk of late perforation. Small bowel contusions larger than 15 mm in diameter had a worse histological grading than those smaller than 15 mm (χ^2 = 0·09, 2 d.f., P = 0·01). Contusions that extended over more than half the bowel circumference (χ^2 = 14·79, 2 d.f., P = 0·0006) and those affecting the mesenteric border (χ^2 = 7·5, 2 d.f., P = 0·024) were more severe injuries. Colonic contusions larger than 20 mm in diameter had a worse histological grading than smaller ones (χ^2 = 14·95, 2 d.f., P = 0·0006). Confluent, rather than diffuse, colonic contusions were more severe injuries (χ^2 = 6·37, 2 d.f., P = 0·04).

Conclusion Once identified at laparotomy, the number of small bowel contusions requiring excision may be reduced from 86 to 60 per cent; similarly, excision of colonic contusions can be reduced from 73 to 27 per cent if small bowel contusions smaller than 15 mm in diameter and colonic contusions of less than 20 mm are managed conservatively.

Involvement of individuals in explosions in civilian or military situations increases steadily. In air, primary blast injuries (caused by the blast wave according to Zuckerman's classification[1]) are anticipated only in those very close to an explosion. Secondary and tertiary injuries (due to energized fragments and bodily displacement respectively) far outnumber primary injuries in most explosions. For this reason, typical primary blast injuries (pulmonary and intestinal contusions) have not been of major clinical significance in most explosions reported in the scientific literature[2–5]. Relatively more primary injury is caused by explosions in enclosed spaces, such as a bus[6] or building[7], and by detonation of modern weapons that generate widespread blast waves[8].

Primary pulmonary and intestinal blast injuries are the most significant lesions; lung contusions, pneumothorax and pulmonary oedema can develop rapidly. The ability to ameliorate pulmonary blast effects using protective materials[9] and to treat mild to moderate pulmonary injury using mechanical ventilation with supplementary oxygen has further heightened the importance of managing the intestinal injury effectively[10].

Exposure to extreme blast overpressure produces immediate intestinal laceration but multiple intestinal contusions or intramural haematomas predominate in non-fatal blast exposures. These lesions, which are morphologically and histologically similar to those caused by blunt abdominal trauma[11], are subject to late perforation. The natural history of the intramural haematoma is uncertain; it is not known which will perforate and which will heal without consequence.

Evidence obtained from small animal experiments, the results of which may lack validity, suggest that contusions larger than 10 mm in mean diameter are at particular risk of delayed perforation and should be excised[12–16]. This study aimed to investigate the relationship between the size and morphology of intramural haematomas and the risk of delayed perforation.

Materials and methods

Twenty-two female Large White pigs weighing 49–66 kg were studied; 16 were exposed to blast and six animals were treated as handled controls. Experimental procedures were conducted in accordance with the provisions of the Animals (Scientific Procedures) Act 1986.

Animals were premedicated with 20 mg droperidol by intramuscular injection before anaesthesia by inhalation of halothane; anaesthesia was continued with intermittent intravenous boluses of sodium pentobarbital. Animals were intubated with a cuffed endotracheal tube (Portex, Hythe, UK) and allowed to breathe spontaneously, supplemented with ventilation by hand as required. While anaesthesia was maintained, all animals underwent tracheostomy to simplify airway care.

An accelerometer in its mount (PCB; Piezotronics, New York, USA) was fixed to the right seventh or eighth rib at the level of the xiphisternum on the side of the animal nearest the blast. Accelerometer readouts enabled measurement of peak thoracic wall acceleration and duration of motion; these variables were recorded primarily for correlation with pulmonary injury severity.

Anaesthesia was maintained by continuous infusion of Sagatal (Rhone-Merieux, Harlow, UK) (17 mg kg^{-1} h^{-1}) before paralysis

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with intravenous pancuronium bromide (0·05 mg kg^{-1} h^{-1}) and ventilation with air to produce normocapnoea (arterial partial pressure of carbon dioxide 5–5·5 kPa). A period of 1 h then elapsed during which baseline values for haemodynamic parameters were established.

To protect from secondary blast injury, pigs were wrapped in a woven aramid blanket, a durable material capable of stopping energized fragments but without blast protective properties. Tertiary blast injury was eliminated by allowing the frame to which the pig was strapped to roll 1·5 m away from the blast before being halted by spring-loaded dash-pots. Just before detonation, sufficient depth of anaesthesia was ensured and ventilation halted in expiration.

Spherical plastic explosive charges weighing between 2·0 and 3·6 kg were detonated at distances of 1·8–3·0 m from the point closest to the animal's chest wall. Explosive conditions were standardized as far as possible and detonation variables were altered in an attempt to obtain uniform pulmonary injury severity. After blast exposure, animals were resuscitated by hand until mechanical ventilation was re-established before transportation to the monitoring facility.

Eight animals were to be monitored for 1 h under continuing anaesthesia before lethal barbiturate overdose. One of these animals died from an undiscovered cause 20 min after blast exposure with pulmonary injuries insufficient to provide a cause of death. Eight animals were monitored for 24 h before lethal injection; all survived for this period.

Urine output was monitored in 24-h experimental animals using a urinary catheter. Basal water and electrolyte requirements were met by intravenous infusion of Ringer's lactate solution (2–4 ml kg^{-1} h^{-1}).

Post-mortem examination and specimen analysis

A midline laparotomy was undertaken immediately after killing to limit the effects of vascular stasis on specimen preparation. After vascular perfusion with dilute barium sulphate suspension (for a separate investigation but which is readily seen on the photomicrographs), intestinal segments bearing intramural haematoma were immersed in 10 per cent formalin. After 24 h of fixation, individual contusions were measured using Johansson's method, in which the square root of the product of the two maximal contusion diameters at right angles to each other represents a single figure assessment of contusion size[12]. Transverse sections of intestine at the midpoint of each contusion were processed in Super Mega-Cassettes (Life Sciences International, Basingstoke, UK) in an enclosed tissue processor (Shandon Hypercenter XP; Shandon Scientific). At the end of the processing schedule, the wax-impregnated tissue was cast into Histoplast wax blocks (Shandon Scientific).

Histological preparation

Transverse sections were cut at a nominal thickness of 8 μm and stained with haematoxylin and eosin before examination by light microscopy.

Statistical analysis

The χ^2 test was used to determine differences between groups of contusions assuming, as the null hypothesis, that histological grades would be evenly distributed between groups. Statistical significance was assumed when $P < 0·05$.

Results

The physical characteristics of blast exposures are detailed in *Table 1*. Overpressure ranged from 383 to 695 (median 482) kPa and peak thoracic wall acceleration from 4·75 to 61·08 (median 21·44) × 10^3 m s^{-2}. All animals sustained only mild pulmonary injury and no animal died from its consequences.

Some 113 1-h contusions (58 small bowel and 55 colonic) and 75 24-h contusions (38 small bowel and 37 colonic) were available for study. Seven contusions (three small bowel and four colonic) were not available for study

Table 1 Animal and blast data for each experiment

					Accelerometer		Overpressure	
Animal no.	Weight (kg)	Charge weight (kg)	Distance (m)	Monitoring time (h)	Peak (× 10^3 m s^{-2})	Positive duration (ms)	Peak (kPa)	Duration (ms)
1	62	3·60	3·0	1	14·72	0·68	—	—
2*	—	2·00	3·0	20 min	8·17	0·83	383	1·40
3	—	2·00	3·0	1	16·64	0·90	432	1·59
4	55	2·00	2·5	24	4·75	0·99	435	0·71
5	57	2·00	2·5	24	19·97	0·83	670	1·04
6	56	—	Control	24	—	—	—	—
7	54	2·00	2·5	1	22·72	0·62	437	1·20
8	53	2·00	2·0	1	15·62	1·01	485	1·70
9	51	2·19	2·4	1	32·67	0·83	601	0·57
10	49	2·19	2·4	1	47·73	0·57	442	0·80
11	50	2·20	2·4	1	21·44	0·88	455	0·67
12	56	2·19	2·4	24	26·98	0·66	482	0·71
13	55	2·19	2·4	24	13·74	1·00	475	0·57
14	52	2·11	1·8	24	61·08	0·40	628	1·62
15	54	2·11	1·8	24	34·52	0·63	695	1·02
16	54	2·05	1·8	24	35·73	0·65	505	0·60
17	50	2·05	1·8	24	—	Atypical trace	601	1·64
18	66	—	Control	24	—	—	—	—
19	50	—	Control	Died at 9 h	—	—	—	—
20	65	—	Control	24	—	—	—	—
21	53	—	Control	24	—	—	—	—
22	53	—	Control	24	—	—	—	—

*Died at 20 min but has been included as a 1-h experiment. Peak overpressures and thoracic wall accelerations were not significantly different in either 1- or 24-h monitoring groups

Table 2 Histological classification of primary intestinal blast injuries

Grade of injury	Mucosal appearance	Muscular appearance	Serosal appearance
I* (*Fig. 1*)	Normal or diffuse bleeding only	Normal	Normal
II	Mucosal haematoma without glandular disruption	Mild oedema only	Normal
III (*Fig. 2*)	Marked haemorrhage with glandular disruption	Marked oedema or minor haemorrhage only	Normal
IV (*Figs 3* and *4*)	Gross glandular or mucosal disruption; muscularis mucosae may be disrupted	Muscular disruption or major haematoma	Subserosal haemorrhage
V	Complete mucosal laceration	Muscular laceration or disruption	Serosal laceration

*Includes contusions in which a submucosal haematoma is evident without other evidence of mural injury

due to technical failure in preparation of the blocks. A median of 11·5 (range 1–31) small bowel and colonic intramural haematomas were sustained in each animal. Modal contusion diameter was between 10 and 20 mm in computed diameter; each animal was at risk of late perforation by the criterion requiring excision of contusions larger than 10 mm. No contusions were found in handled controls.

Histological features of the intramural haematoma fell into defined patterns and were classified according to the scheme represented in *Table 2* and *Figs 1–4*. This classification divides histological features into groups I–V; grades I and II, and IV and V respectively were combined to represent groups at low risk and high risk of late perforation. When different grades could be ascribed to different layers, the highest overall grade was applied to each contusion. In general, less severe injuries were focused on the mucosa; as injury severity increased, so the deeper layers of the intestinal wall were progressively damaged. The most severe forms of injury were immediate full-thickness perforation (seen in only two instances) and lacerations of the muscularis propria, which would have been likely to result in early perforation. Most injuries were low risk but 16 per cent of small bowel and 12 per cent of colonic contusions were at high risk of late perforation (*Table 3*).

Macroscopic features of individual contusions were correlated with histological grading to establish patterns of injury that could be predictive of an increased risk of late perforation. The features of individual contusions

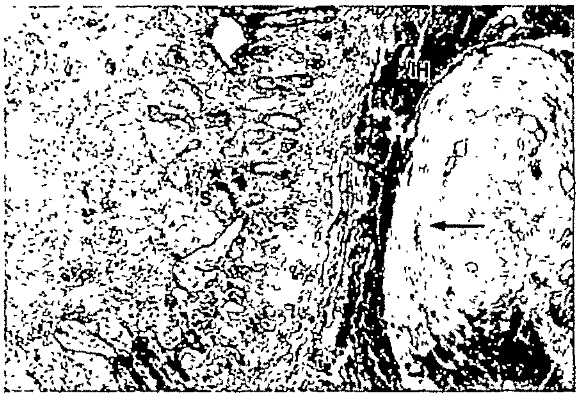

Fig. 2 Grade III injury to colon (24-h contusion, 30 × 15 mm, 8-μm thick, haematoxylin and eosin stain, original magnification × 31). The striking feature of this micrograph is the loss of mucosal structure (S) with the appearance of inflammatory cell infiltrate into the layer (★). A narrow intramural haemorrhage (IH) is seen in the submucosa. The muscle layers show mild oedema (→) but no evidence of more severe injury

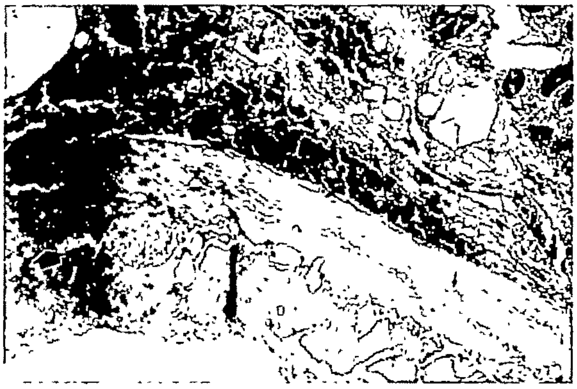

Fig. 1 Grade I injury to small bowel (24-h contusion, 35 × 20 mm, 8-μm thick, haematoxylin and eosin stain, original magnification × 31). At this point of the intramural haematoma, the blood has separated into red cell aggregates and serum (★), a feature testifying to the rapidity of accumulation of the haemorrhage. The muscular layers at this point show very mild oedema (→), evidenced by loosening of the cellular structure and the accumulation of a few inflammatory cells in the intermuscular plane (⧫). No muscle disruption is seen on this slide

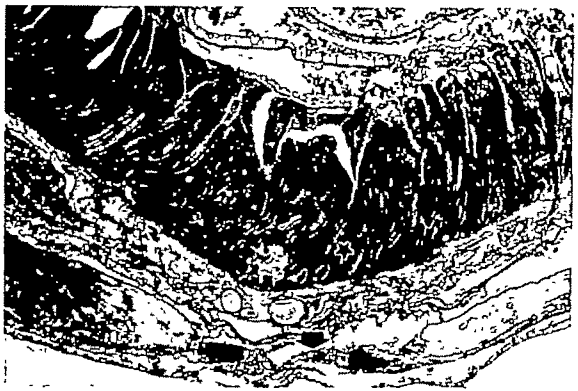

Fig. 3 Grade IV injury to small bowel (20-min contusion, 20 × 15 mm, 8-μm thick, haematoxylin and eosin stain, original magnification × 62·5). This section was taken from an area of full-thickness injury. Marked haemorrhage can be seen in the mucosa (★) with loss of structure; the muscularis mucosae may also be disrupted in places. Mild haemorrhage is present in the submucosa. The muscular layers are severely injured with physical disruption of muscle and serosa (⧫). Adjacent to these areas the muscle is oedematous. This lesion is at very high risk of perforation

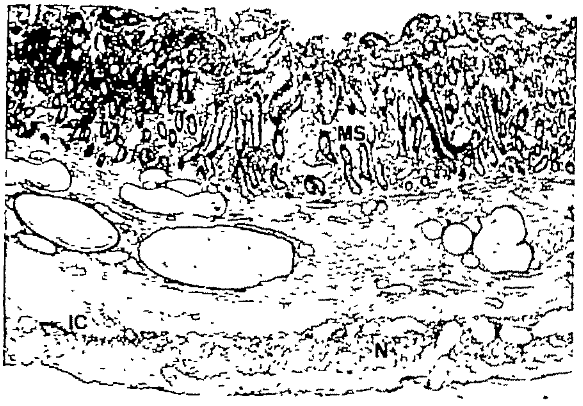

Fig. 4 Grade IV injury to small bowel (24-h contusion, 50 × 40 mm, 8-μm thick, haematoxylin and eosin stain, original magnification × 31). This injured section shows evidence of injury in all layers of the bowel wall. The mucosa is congested, contains diffuse haemorrhage and is disrupted in the superficial layers (MS). Oedema and haemorrhage are seen in the submucosa, but most striking is the muscular oedema and disruption, most marked in the outer longitudinal layer (N). Also seen is the increase in inflammatory cells (IC) in the muscular layers in particular and in the plane between them. In this section the muscles are necrotic; the contusion is at very high risk

considered to be most easily assessed at laparotomy *in vivo* were size, position relative to the intestinal mesentery, extent of the intramural haematoma relative to the intestinal circumference at that point, and whether or not the pattern of haemorrhage appeared diffuse or confluent. Comparison of histological grade with these external features is shown in *Table 4*.

Small bowel contusions larger than 15 mm had a significantly worse histological grading than smaller ones ($\chi^2 = 9{\cdot}09$, 2 d.f., $P = 0{\cdot}01$). Those that extended over more than half the bowel circumference ($\chi^2 = 14{\cdot}79$, 2 d.f., $P = 0{\cdot}0006$) and those affecting the mesenteric border ($\chi^2 = 7{\cdot}5$, 2 d.f., $P = 0{\cdot}02$) were more severely injured. Colonic contusions larger than 20 mm in diameter had a significantly worse histological grading than smaller ones ($\chi^2 = 14{\cdot}95$, 2 d.f., $P = 0{\cdot}0006$). Confluent, rather than diffuse, colonic contusions were more severely injured ($\chi^2 = 6{\cdot}37$, 2 d.f., $P = 0{\cdot}04$).

Table 3 Distribution of blast intestinal contusions by age and histological grade

	Contusion grade					
	I	II	III	IV	V	Total
Small bowel						
1 h	26	12	10	10	0	58
24 h	9	12	12	3	2	38
Colon						
1 h	25	15	6	9	0	55
24 h	28	6	1	2	0	37

Combination of grades I and II as low risk and grades IV and V as high risk for late perforation shows no significant difference between histological grades at 1 and 24 h. For the small bowel $\chi^2 = 2{\cdot}69$, 2 d.f., $P = 0{\cdot}26$, and for the colon $\chi^2 = 5{\cdot}19$, 2 d.f., $P = 0{\cdot}08$

Table 4 Distribution of histological grades between contusion groups of different external appearance

	Histological grade			Significance		
Contusion parameter	I and II	III	IV and V	χ^2	d.f.	P
Size (mm)						
Small bowel						
≤15	30	5	3	9·09	2	0·01
>15	28	17	13			
Colon						
≤20	60	4	3	14·95	2	0·0006
>20	14	3	8			
Position						
Small bowel						
Mesenteric	18	12	11	7·5	2	0·02
Antemesenteric	39	10	6			
Colon						
Mesenteric	8	1	1	0·12	2	0·94
Antemesenteric	66	6	10			
Circumferential extent*						
Small bowel						
One-half or less	47	13	6	14·79	2	0·0006
More than one-half	10	9	11			
Confluence						
Small bowel						
Confluent	22	11	12	5·49	2	0·06
Diffuse	35	11	5			
Colon						
Confluent	26	4	8	6·37	2	0·04
Diffuse	48	3	3			

*The relationship between grade and circumferential extent is not shown for the colon because only two contusions were larger than half the circumference – a feature more to do with colonic, rather than contusion, size

Discussion

In contrast to other experimental evidence of risk of late perforation caused by intramural haematoma, a method of injury consistent with the blast effect has been studied in an animal model of similar size and physiological behaviour to that of an adult human. The information derived is likely to be applicable to a human. Readily recognizable features were identified *in vivo* which alert the clinician to the presence of a high-risk mural injury in contrast to the innocent accumulation of blood in the submucosal plane (the most common pattern of injury).

The classification of intestinal blast contusions has been hampered by the recognized difficulties surrounding the development of a suitable model of this injury. The data have been established by histological examination of a large number of contusions 1 and 24 h after blast injury. Although the usual interval for perforation is between 1 and 14 days, this study has identified patterns of injury and a classification in which no difference was observed between the distribution of histological grades at the two times (*Table 3*). Subsequent analysis, therefore, has been without regard to the age of the contusion. The ability of the classification to identify early features of injury predictive of perforation is suggested by the appearance of necrosis and inflammatory cell infiltrate in some injuries examined at 24 h. The wide range of injury severity is consistent with a variable interval before perforation and a natural history that includes resolution of injury without clinical consequence in low-risk contusions.

If these experimental guidelines were adopted and small bowel contusions less than 15 mm in diameter and colonic contusions smaller than 20 mm were left alone, the number of small bowel contusions requiring excision would be reduced by one-quarter and colonic contusions by two-thirds (*Table 5*). Utilizing the other prognostic features described may reduce this further.

Surgeons will encounter intestinal contusions in one of two ways. Blast-affected casualties will present either without need for immediate laparotomy, in which case awareness of the potential for late perforation will be important in the clinical management, or the need for operative treatment will be clear. These guidelines are expected to have their main application in the latter case. Intramural haematomas of all sizes are at risk of late perforation by this analysis, and some very large contusions are histologically innocent and thus have a good prognosis (*Table 4*). Clearly, blanket application of the size criteria would result in both overtreatment of simple submucosal haemorrhage and undertreatment of small high-risk contusions.

Table 5 Effect of adopting present study guidelines on intramural haematomas that require excision

	No. excised	
	Small bowel	Colon
Previous size criterion		
10 mm	83 of 96 (86)	67 of 92 (73)
Present size criteria		
15 mm	58 of 96 (60)	—
20 mm	—	25 of 92 (27)

Values in parentheses are percentages

Consideration of the mechanisms of injury in intestinal blast trauma may help to identify contusions at greatest risk more accurately. This histological classification is consistent with a mechanism of injury producing damage to the mucosa in the first instance. Practical studies of blast and blunt abdominal injury show that some intestinal injury is caused by the passage of pressure waves through the abdomen[17,18]. Such waves theoretically injure by a mechanism termed spalling (physical disruption of the surface of a dense material when stress waves are reflected as tensile waves on their passage to a less dense medium). The spectrum of intestinal injury identified here is consistent with injury directed from mucosa to serosa, i.e. injury caused by the release of energy in the mucosa initially and, if energy transfer is sufficient, progressive disruption of the submucosal, muscular and serosal layers. Serosal injury is, therefore, *de facto* evidence of transmural injury, indicating a contusion at high risk.

Simple size guidelines such as these are insufficiently accurate for application as the sole discriminator for excision of intramural haematomas. Further investigations are certainly warranted to check the accuracy of the treatment thresholds and to establish whether injury to the seromuscular layer is the most important feature. These studies would be appropriately undertaken in longer-term experiments.

An important feature of these results was that histological severity did not always correlate with contusion size. The appearance of submucosal haemorrhage may only be a marker for significant injury and not the most important feature in its own right. The variable appearance of single cell death, or apoptosis, was observed predominantly in the epithelium and lamina propria of many of the sections. This has not been reported here because other, more obvious, poor prognostic features have been identified. It is probable that apoptosis is another marker of absorption of energy at the point of contusion.

This study has identified external appearances of blast intestinal contusions that may be associated with a higher risk of delayed perforation. These relationships demand further investigation to establish whether they can help to limit morbidity and mortality due to intestinal perforation after blast exposure.

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Surgical workshop

Anchoring fixation suture to secure Broviac catheters

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Broviac catheters have been used for the administration of nutrient solution or chemotherapeutic agents. The ingrowth of fibrous tissue into the Dacron (Du Pont, Wilmington, Delaware, USA) cuff provides the necessary stabilization but this process takes a few weeks to occur. Patients with this catheter are often malnourished and some are receiving chemotherapy and/or steroid so the normal wound healing process might be impaired.

The frequency of catheter dislodgement is not rare[1,2] and various methods of fixation of the cuff have been suggested[1,3–5]. A procedure for securing central venous catheters is described called 'anchoring fixation suture' technique.

Surgical technique

A pair of long forceps is introduced into the subcutaneous space from a cut down incision and tunnelled to the anterior chest wall. The catheter is grasped, and the needle with 3/0 nylon suture is inserted ensuring that it loops around the forceps at 2 cm from the exit site (*Fig. 1*).

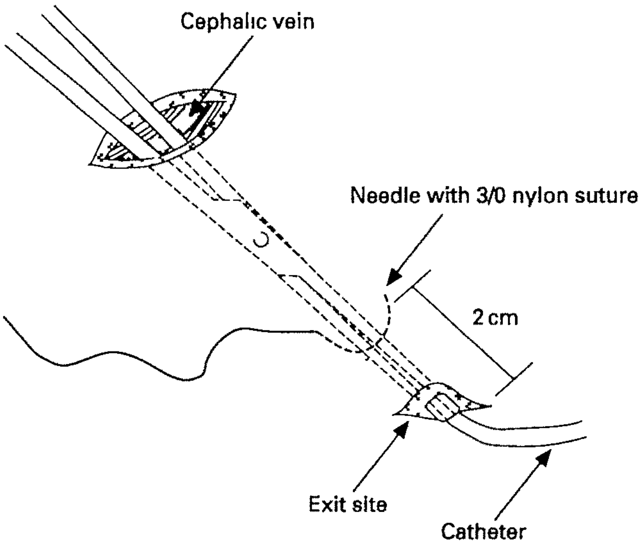

Fig. 1 Anchoring fixation suture technique; anchoring

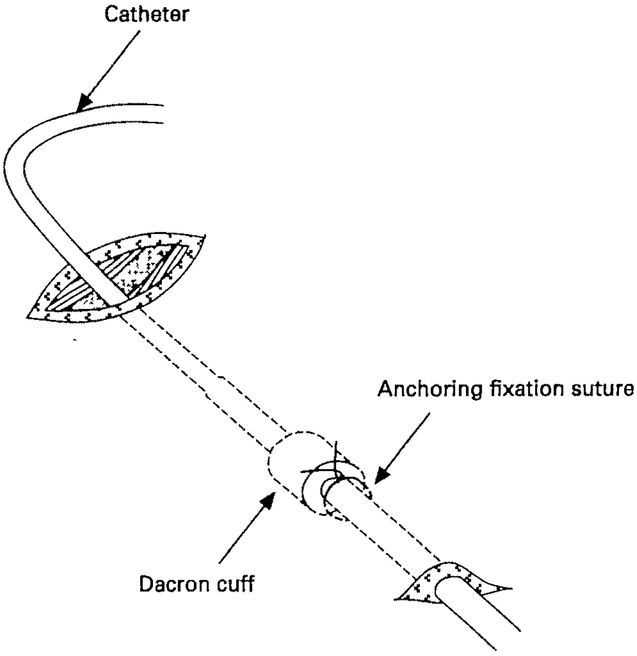

Fig. 2 Anchoring fixation suture technique, tied

After the catheter is brought through and the cuff pulled into the tunnel, the suture is tied as an anchor. The catheter is secured to this tied anchor fixation by pulling caudally (*Fig. 2*). The catheter is cut to the proper length and inserted into the vein.

The incision wounds are sutured. A suture on the outside of the tunnel is used to secure the catheter on to the chest wall.

Discussion

This 'anchoring fixation suture' technique has several advantages over other methods. Additional paraphernalia[3,5] to secure the catheter is not required. An additional incision is not needed. There is no possibility of damaging the catheter. There have been no accidental dislodgements using this approach.

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Comparison of five systems for staging lymph node metastasis in gastric cancer

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Background There are several systems for staging lymph node metastasis in gastric cancer. Their relative merits are not clear.

Methods In this retrospective analysis, the nodal status was classified according to the Union Internacional Contra la Cancrum (UICC) and Japanese staging systems, the number and frequency of lymph node metastasis, and the level of involved nodes. Each staging system was scored as good (+1), fair (0) or poor (−1) with respect to prognostic value, theoretical value, convenience, reproducibility and surgical applicability.

Results There were no differences between the five staging systems in predicting survival. The Japanese staging system was most arbitrary owing to the complexity of the system, although it had an advantage in surgical application. The same disadvantage was found in the UICC system and the level system. Determination of the number and frequency of involved nodes was convenient and reproducible, but the number of lymph nodes dissected must be considered when the number of positive nodes is used for staging.

Conclusion The classification of metastasis to the regional lymph nodes as N_0 (no nodal metastasis), N_1 (metastasis in 1–25 per cent of dissected nodes) and N_2 (metastasis in more than 25 per cent of dissected nodes) would be a simple, convenient, reproducible staging system with an ability to predict surgical results.

There are several systems for the staging of lymph node metastasis in gastric cancer. In the Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) system[1], metastasis of gastric cancer to the regional lymph nodes is classified according to the location and distance of the metastatic lymph nodes from the edge of the primary tumour. Under the general rules for gastric cancer study in surgery and pathology of the Japanese Research Society for Gastric Cancer (JRSGC), the regional lymph nodes of the stomach are numbered according to their anatomical locations. Patients are also classified into group 1, 2 or 3 according to the site of the tumour in the stomach[2]. Adachi *et al.*[3] proposed a classification of lymph node level in gastric cancer: level 1 (perigastric) nodes, level II (intermediate) nodes, and level III (distant) nodes, irrespective of the location of tumours. Some authors have reported the superiority of quantitative staging systems, such as the number of metastatic lymph nodes[4,5] and the ratio of invaded to removed nodes[6,7].

In this study, these five different systems for staging nodal status in gastric cancer were compared for their ability to predict survival and to reflect anatomical pathways of lymphatic spread, and for their simplicity, arbitrariness and surgical application. Based on this analysis, a simple classification of lymph node metastasis in gastric cancer is proposed.

Patients and methods

Patients

D_2 or more extended lymph node dissection with total or subtotal gastrectomy was performed in 886 patients with gastric cancer (584 men, 302 women) between January 1985 and December 1994 In 723 cases (81·6 per cent) operation was performed with curative intent. The definition of a curative operation according to the Korean Research Association for Gastric Cancer includes no distant metastasis, no residual tumour at both resection margins, T_3 or complete resection of T_4, no gross residual tumour, and lymphadenectomy of D_2 or greater

Lymphadenectomy map

A lymphadenectomy map was made for each patient, including the number of involved and uninvolved lymph nodes at specific locations. For the classification of nodal status, the perigastric lymph nodes along the lesser and greater curvatures (from number 1 to number 6 of the JRSGC system) were subdivided into two categories according to the distance from the edge of the primary tumour as: subdivision -1, nodes within 3 cm of the edge of the tumour; and subdivision -2, nodes more than 3 cm from the edge of the tumour. The nodes located along the left gastric, common hepatic, coeliac and splenic arteries, and distant intra-abdominal lymph nodes, were numbered as in the JRSGC system (7–16).

Classification of nodal status

Nodal status was classified according to the UICC TNM staging system[1] and the general rules for gastric cancer study in surgery and pathology of the JRSGC[2]. The level of lymph node metastasis was classified according to Adachi *et al.*[3] as: N_0, no lymph node metastasis; N_1, metastasis in perigastric lymph nodes; N_2, metastasis in intermediate nodes; and N_3, metastasis in distant lymph nodes irrespective of the location of tumours; and according to the number of lymph nodes involved by metastases and the frequency of lymph node metastasis, as shown in *Table 1.*

Comparison of staging systems

Each staging system was scored as good (+1), fair (0) or poor (−1) with respect to prognostic value (ability to predict survival

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Table 1 Methods of lymph node status classification

Lymph node metastasis	N_0	N_1	N_2	N_3
Level	None	Perigastric	Intermediate	Distant
Number	None	1-3	4-6	>6
Frequency (%)	None	≤25	26-50	>50

rate), theoretical value (ability to reflect anatomical pathways of lymphatic spread), convenience (simplicity), reproducibility (degree of arbitrariness) and surgical applicability (level of lymph node dissection).

Statistical analysis

Survival rates were calculated with the Kaplan-Meier method, and the difference between each group was evaluated by the log rank method. Follow-up data were available for 871 (98·3 per cent) of the 886 patients. Some 270 patients died from gastric cancer.

Results

A lymphadenectomy map was available for every patient. The number of dissected lymph nodes per patient varied widely (9-123), with a mean of 39·3. The number of patients in each group, according to the five staging systems, is shown in *Table 2*. *Table 3* presents 5-year survival rates in relation to the categories of lymph node metastasis according to each system. Survival distributions of patients are illustrated according to the UICC N classification (*Fig. 1*), the JRSGC N classification (*Fig. 2*), the level of involved lymph nodes (*Fig. 3*), the number of involved lymph nodes (*Fig. 4*) and the frequency of involved lymph nodes (*Fig. 5*). The figures demonstrate that each staging system was able to identify significant differences in survival among subgroups of patients.

The results given below are summarized in *Table 4*. Because the general rules for gastric cancer study in surgery and pathology of the JRSGC are based on the lymphatic pathway from the upper, middle and distal third of the stomach, this staging system had a good theoretical advantage. The UICC TNM system and the level system had fair theoretical advantages because the location of metastatic lymph nodes was considered. The quantitative system (number or frequency) had no consideration for the lymphatic pathway. It was sometimes difficult to divide

Table 2 Number of patients in each nodal group according to five staging systems ($n = 886$)

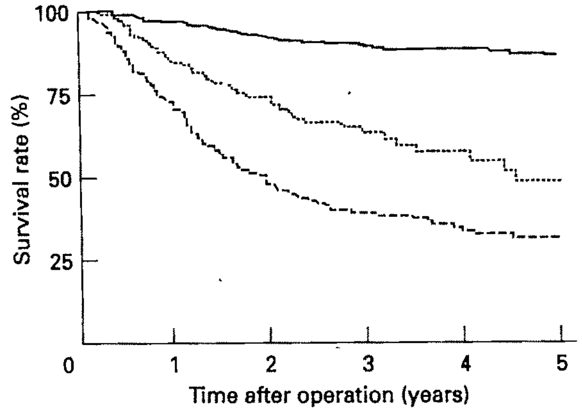
System	N_0	N_1	N_2	N_3
UICC	439*	115	332	0
JRSGC	436	236	116	98
Level	436	187	176	87
Number	436	152	88	210
Frequency	436	301	80	69

UICC, Union Internacional Contra la Cancrum; JRSGC, Japanese Research Society for Gastric Cancer. *Three cases of skip metastases (one hepatic artery proper, one mid-colic and para-aortic, one para-aortic lymph node metastasis)

Table 3 Five-year survival rate of each group of patients ($n = 886$)

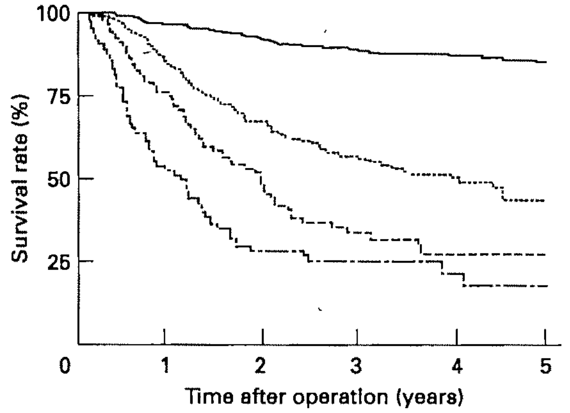
	5-year survival rate (%)				
System	N_0	N_1	N_2	N_3	P*
UICC	85·1(2·2)	48·2(6·8)	31·2(3·5)	—	0·0001
JRSGC	85·6(2·2)	45·0(4·7)	28·7(5·5)	19·2(5·8)	0·0001
Level	85·6(2·2)	51·4(5·2)	25·9(4·8)	18·9(6·0)	0·0001
Number	85·6(2·2)	52·2(5·9)	52·0(6·3)	14·3(3·8)	0·0001
Frequency	85·6(2·2)	46·9(4·1)	12·6(6·6)	7·3(4·2)	0·0001

Values in parentheses are standard errors. UICC, Union Internacional Contra La Cancrum; JRSGC, Japanese Research Society for Gastric Cancer. *Log rank test



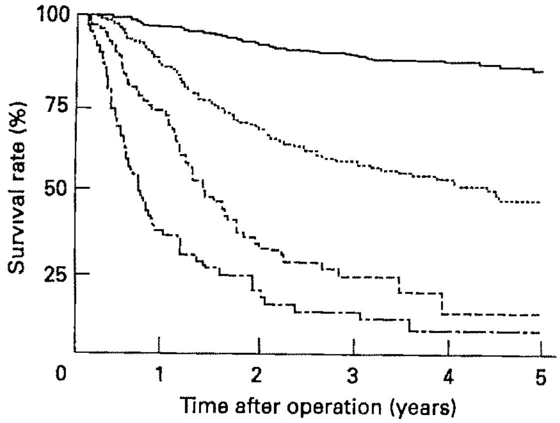
No. at risk						
N_0	439	388	290	214	152	98
N_1	115	89	58	36	23	13
N_2	332	215	114	67	33	19

Fig. 1 Survival distribution of patients according to the Union Internacional Contra la Cancrum nodal (N) classification: ——, N_0; ·····, N_1; – – – –, N_2. $P = 0{\cdot}0001$, log rank test



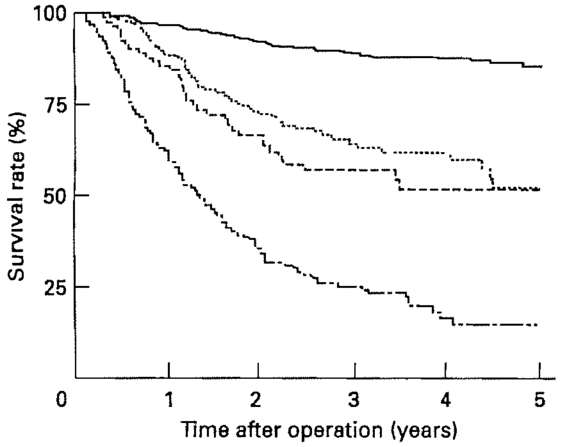
No. at risk						
N_0	436	385	290	214	152	98
N_1	236	182	114	72	40	21
N_2	116	79	38	21	10	6
N_3	98	46	20	15	6	5

Fig. 2 Survival distribution of patients according to the Japanese Research Society for Gastric Cancer nodal (N) classification: ——, N_0; ·····, N_1; – – – –, N_2; – · – · –, N_3. $P = 0{\cdot}0001$, log rank test



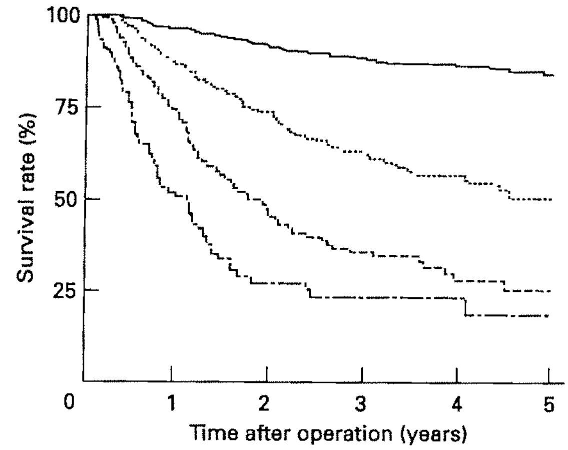
No. at risk						
N_0	436	385	290	214	152	98
N_1	187	150	99	62	36	18
N_2	176	118	58	32	15	10
N_3	87	39	15	9	5	4

Fig. 3 Survival distribution of patients according to the level of lymph node metastasis. ——, N_0 (level 0, no lymph node metastasis); ·····, N_1 (level I, metastasis in perigastric lymph nodes); – – – –, N_2 (level II, metastasis in intermediate lymph nodes); — · — · —, N_3 (level III, metastasis in distant lymph nodes) $P = 0{\cdot}0001$, log rank test



No. at risk						
N_0	436	385	290	214	152	98
N_1	152	120	81	51	34	17
N_2	88	71	43	28	13	8
N_3	210	116	48	24	9	7

Fig. 4 Survival distribution of patients according to the number of lymph nodes with metastasis. ——, N_0 (no lymph node metastasis); ··· ·, N_1 (metastasis in 1–3 lymph nodes); – – – –, N_2 (metastasis in 4–6 lymph nodes); — · — · —, N_3 (metastasis in more than 6 lymph nodes). $P = 0{\cdot}0001$, log rank test



No. at risk						
N_0	436	385	290	214	152	98
N_1	301	235	145	88	52	29
N_2	80	51	18	9	2	2
N_3	69	21	9	6	2	1

Fig. 5 Survival distribution of patients according to the frequency of lymph node metastasis. ——, N_0 (no lymph node metastasis); ·····, N_1 (metastasis in 1–25 per cent of dissected lymph nodes), – – – –, N_2 (metastasis in 26–50 per cent of dissected lymph nodes); — · — · —, N_3 (metastasis in more than 50 per cent of dissected lymph nodes). $P = 0{\cdot}0001$, log rank test

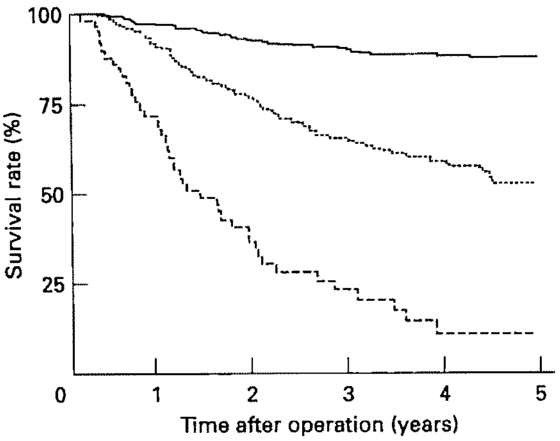
Table 4 Summary comparison of the five staging systems

Criterion	UICC	JRSGC	Level	Number	Frequency
Prognostic	Good	Good	Good	Good	Good
Theoretical	Fair	Good	Fair	Poor	Poor (fair*)
Convenient	Fair	Poor	Fair	Good	Good
Reproducible	Fair	Poor	Fair	Good	Good
Surgical	Fair	Good	Fair	Poor	Fair (good*)
Score	+1	+1	+1	+1	+2 (+4*)

UICC, Union Internacional Contra la Cancrum; JRSGC, Japanese Research Society for Gastric Cancer. *In case of D_2 or more extended lymphadenectomy

certain lymph nodes into the correct tier. In contrast to the ability to reflect the lymphatic pathway, the quantitative system was convenient and reproducible because it had no consideration for the location of the tumour and lymph node. The JRSGC system was very complicated, and the other two systems ranked fair in this respect. From the viewpoint of surgical application, the JRSGC system was the best. Since the Japanese reports of the early 1970s, surgery for gastric cancer has evolved toward a locoregional approach with systematic lymph node dissection. This systematic surgery has contributed, at least partly, to improvements in survival. The level of lymphadenectomy, such as D_1, D_2, D_3 or D_4, was classified according to the JRSGC system. The number system was ranked poorly because there was a great variation in the number of dissected lymph nodes per patient. The frequency system ranked fair because it took account of the number of dissected lymph nodes. The UICC system and level system also ranked fair, because they took into consideration the location of metastatic lymph nodes.

Besides the variation in the number of dissected lymph nodes per patient, D_2 or more extended lymph node dissection was a requisite for the criterion of curative gastrectomy. Five-year survival rates were similar among groups N_2 and N_3 of the frequency system, so that the lymph node status of the gastric cancer could be classified into three groups according to the ratio of metastatic to dissected regional lymph nodes (perigastric nodes along the lesser and greater curvatures, the nodes located along the left gastric and common hepatic, splenic and coeliac



No. at risk						
N_0	426	377	285	212	150	98
N_1	237	198	128	79	48	26
N_2	60	38	17	9	3	3

Fig. 6 Survival distribution of patients after curative resection according to the ratio of metastatic to dissected regional lymph nodes (perigastric nodes along the lesser and greater curvatures, the nodes located along the left gastric and common hepatic, splenic and coeliac arteries) ——, N_0 (no regional lymph node metastasis); ····, N_1 (metastases found in 1–25 per cent of dissected lymph nodes); – – – –, N_2 (metastases found in more than 25 per cent of dissected regional lymph nodes irrespective of the location of tumours or lymph nodes). $P = 0{\cdot}0001$, log rank test

arteries). The frequency of involved lymph nodes was classified into categories of 0 per cent (N_0), 1–25 per cent (N_1) and greater than 25 per cent (N_2) irrespective of the location of tumours or lymph nodes; the 5-year survival rates after curative surgery were 87·6, 53·2 and 11·4 per cent respectively ($P = 0{\cdot}0001$, *Fig. 6*).

Discussion

There are several purposes for tumour staging: (1) to assist in the definition of clinical management; (2) to facilitate communication between physicians; (3) to provide a basis for stratification and analysis of treatment results in prospective studies; and (4) to provide some prognostic information for patients and their families[8]. To accomplish these purposes, the staging system must be both simple and scientific.

The five systems for staging lymph node metastasis in gastric cancer all identified significant differences in survival between subgroups of patients.

The UICC TNM system and the level system received similar scores, whereas the JRSGC system reflected anatomical pathways of lymphatic spread and was a good guide of the level of lymph node dissection, but was very complicated. The quantitative system (number or frequency) was not an artificial classification and could give precise information for prognosis without the problems related to nodal staging. To overcome a weak point of this system in surgical application, D_2 lymphadenectomy was a prerequisite (i.e. lymphadenectomy including all perigastric lymph nodes along the lesser and greater curvatures and the nodes located along the left gastric and common hepatic, splenic and coeliac arteries).

Although opinions differ as to the relative importance of the number *versus* the anatomical level of metastatic lymph nodes[9], there have been many reports on quantitative analysis (number and/or frequency) of metastatic lymph nodes in gastric cancer[4–7,10–13]. These reports have emphasized the importance of nodal involvement irrespective of site. The present study showed that the 5-year survival rate after gastrectomy progressively decreased with an increasing frequency of nodal metastases (N_0 to N_2), as shown in *Fig. 6*. Roder *et al.*[7] reported a significant deterioration in the prognosis when more than 20 per cent of removed lymph nodes were invaded. However, many other authors[6,11] have shown a similar deterioration in the prognosis when 25 per cent of the removed lymph nodes were positive, as does the present study. Because this ratio can be influenced by the number of surgically removed lymph nodes, a wide lymph node dissection undoubtedly improves the accuracy of the staging as well as the prognosis in patients with early lymphatic metastases. If the lymph node examination is insufficient, the nodal stage can erroneously be listed as earlier, and the outcome of patients apparently becomes less favourable for that particular stage (stage migration phenomenon[14] or the Will Rogers effect[15]). The independent prognostic impact of nodal status is given at the beginning of therapy and cannot be influenced by surgical therapy. However, from the surgical point of view, the prognosis can be improved by complete resection of the primary tumour and its lymphatic drainage (expressed by the lymph node ratio)[7].

In summary, the lymph node status of gastric cancer can be classified into three groups according to the ratio of metastatic to dissected regional lymph nodes: N_0, no metastasis; N_1, metastasis in 1–25 per cent of regional lymph nodes; N_2, metastasis in more than 25 per cent of regional lymph nodes, irrespective of the location of tumours or lymph nodes. This staging system is simple and gives precise information for prognosis without the problems related to nodal staging.

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Amylase concentration of drainage fluid after total gastrectomy

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Background Pancreatic fistula is a serious complication of total gastrectomy with splenectomy. The amylase content of drainage fluid was examined and its usefulness for predicting pancreatic complications after gastrectomy was evaluated.

Methods The amylase concentration of the fluid in the peripancreatic drain was determined prospectively in 102 patients who underwent total gastrectomy in 1995.

Results Pancreatic fistula developed in 13 patients, whose drainage fluid amylase levels on the first postoperative morning were significantly higher than those of patients without fistula formation. Among 27 patients with amylase levels exceeding 4000 units, eight later developed pancreatic fistula, while only five (7 per cent) of 68 with amylase levels below 4000 units did so. All complications were successfully managed and there were no deaths.

Conclusion Determination of drainage fluid amylase levels is a simple and useful method for the prediction of pancreatic fistula formation and may help to plan appropriate management.

Total gastrectomy with systematic lymphadenectomy for gastric cancer is a major abdominal operation associated with high morbidity and mortality rates[1–3]. Splenectomy with distal pancreatectomy in this operation appears to be responsible for most complications. Pancreatic leakage and fistula formation are particularly serious and potentially fatal.

The ideal means of avoiding pancreatic injury is, of course, not to touch the pancreas, leaving the lymph nodes near this organ intact. However, the nodes along the splenic artery and in the splenic hilum often show involvement in proximal gastric carcinoma, and dissection of these positive nodes has been demonstrated to be associated with survival benefits[4]. In addition, gastric tumours occasionally invade the pancreas directly, making combined resection unavoidable for complete removal of the tumour. Therefore, partial resection or at least mobilization of the pancreas is often required for radical gastrectomy, and may increase the risk of subsequent complications.

Prevention of deaths associated with pancreatic leakage mandates effective drainage. Drains placed near the pancreas serve not only as a drainage route but also provide information about pancreatic leakage. In the present study the amylase content of drainage fluid after total gastrectomy was determined prospectively. The usefulness of this clinical parameter for the prediction of complications was evaluated.

Patients and methods

In 1995, 102 patients with gastric malignancy (95 carcinomas and seven lymphomas) underwent total gastrectomy at this hospital. These cases accounted for 33 per cent of the 308 gastric operations performed in 1995. All 102 total gastrectomies were performed or supervised by one of four staff surgeons. The oesophagojejunal anastomosis was made using a circular stapler in all cases. No somatostatin analogues were used. All patients received total parenteral nutrition after operation.

At operation drainage tubes were placed as follows. After completion of intestinal reconstruction the abdominal cavity was washed with 3 litres of warm saline and three duple-type drains were placed: one in the foramen of Winslow, one near the oesophagojejunostomy and the third in the left subphrenic space.The last drain was placed dorsal to the pancreatic tail in cases with pancreatic mobilization. In those requiring partial pancreatectomy, another or one of the above-mentioned drains was placed near the pancreatic stump. Each drain was connected to a bottle through an extension tube. Early on the first postoperative morning, 2 ml of discharge in the extension tube was collected from each drain for determination of amylase content. The highest amylase value among the three (or four) drains, usually that of the left subphrenic drain, was taken as the representative value for the study. Serum amylase levels were also determined on the first postoperative day

The operation records of these 102 patients were examined to evaluate the surgical details: length of operation, blood loss, extent of lymphadenectomy, presence or absence of pancreatic mobilization and/or splenectomy. The postoperative course of each patient was assessed according to the presence or absence of pancreatic fistula. Pancreatic fistula was defined as a condition in which fluid with an amylase concentration more than three times the normal serum concentration drained from the peripancreatic area for more than 7 days after operation.

Surgical procedures and pathological findings were recorded according to the Japanese Classification of Gastric Carcinoma[5]. For statistical analysis, the Mann–Whitney U test, χ^2 test and Fisher's probability test were used. Differences were considered significant at $P<0.05$.

Results

The clinicopathological features of the 102 patients are summarized in *Table 1*. There were seven lymphomas (six stage IE, one stage IIE). The operation was undertaken with curative intent in 84 patients and was palliative in 18. The standard D_2 lymphadenectomy was performed in 52 cases, with more extensive dissection in 30. Lymphadenectomy was limited (D_0 or D_1) in 20 patients, mostly because of high operative risks or very advanced tumours. Mean operating time was 273 (range 110–550) min. Mean blood loss was 690 (range 101–4457) ml. Blood transfusions were needed in 16 cases. Reconstruction was by Roux-en-Y ($n = 85$) or by jejunal interposition ($n = 17$).

Anastomotic failure of the oesophagojejunostomy occurred in one patient who was treated conservatively.

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Table 1 Clinicopathological features of 102 patients who underwent total gastrectomy

Mean (range) age (years)	59·6 (24–88)
Sex ratio (M:F)	72:30
Carcinoma*	
t_1	29
t_2	11
t_3	43
t_4	12
n_0	34
n_1	15
n_2	19
n_{3-4}	27

*Ninety-five cases according to the Japanese classification

Table 2 Incidence of pancreatic fistula according to the drainage fluid amylase level on the first postoperative day

Drain amylase (units)	No. of patients	Pancreatic fistula
<1000	24	1
1000–2000	24	1
2000–4000	20	3
>4000	27	8
Total	95*	13 (14)

Values in parentheses are percentages. *Drainage fluid amylase concentration was not determined on the first day in seven of the 102 patients

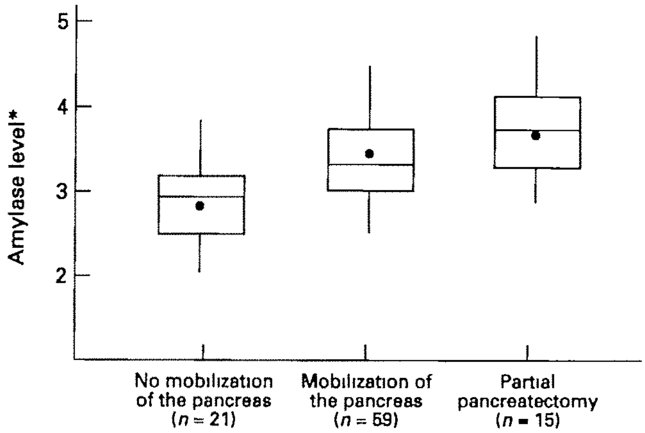

Fig. 1 Boxplot of drainage amylase concentration according to the degree of manipulation of the pancreas. Boxes show the median and interquartile range. Whiskers are extended to the most distant value within the 1·5 interquartile range from the median. Solid circles within the boxes represent mean values. *Logarithm of the amylase concentration in international units

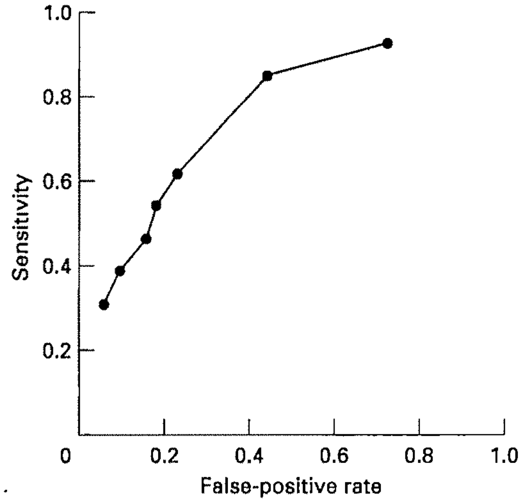

Fig. 2 The receiver–operator characteristic curve of drainage amylase level and pancreatic fistula formation. The points represent the cut-off levels of (from the upper right) 1000, 2000, 4000, 6000, 8000, 10 000 and 20 000 units

Two patients developed leakage at the duodenal stump without evidence of preceding pancreatic leakage. There were no operative deaths. One patient died 40 days after operation due to the unusually rapid growth of an α-fetoprotein-producing gastric tumour after non-curative resection.

The pancreas was mobilized along with the spleen in 77 patients, and splenectomy was carried out in 79. Although pancreatectomy was also necessary due to direct tumour invasion in 15 of 79 patients, the pancreas was usually preserved according to Maruyama and colleagues' method[6]; briefly, the pancreatic body was fully mobilized and the splenic artery was ligated and cut near its origin. The lymph nodes along the splenic artery and splenic hilum were meticulously dissected *en bloc*, the entire pancreas being preserved. Pancreas-preserving splenectomy required a significantly longer operating time (mean 273 min) and involved greater blood loss (mean 696 ml) than the operation without splenectomy (mean 222 min and 405 ml; $P < 0{\cdot}01$, Mann–Whitney U test).

Pancreatic fistula with infections of variable severity occurred in 13 cases. One patient experienced an arterial rupture requiring emergency laparotomy. All others were managed conservatively with elaborate drain management. This included frequent radiological tests through drains to evaluate abscess formation; exchange of drains from duple type to double-lumen type for continuous irrigation or suction; and change of tube location for optimal drainage, sometimes under fine fibrescopic guidance. The mean postoperative hospital stay for these 13 patients was 39 days, whereas that of the remaining patients was 26 days. Of the 13 patients with pancreatic fistula, 12 had undergone splenectomy with pancreatic mobilization. The incidence of pancreatic fistula in patients who had pancreatectomy (three of 15) was not significantly higher than that of those without pancreatectomy (ten (11 per cent) of 87; $P = 0{\cdot}40$, Fisher's test).

Drainage amylase levels were determined in 95 patients on the first postoperative day, but, for technical reasons, not until the second day in seven patients. None of the latter patients developed pancreatic complications, and all seven were excluded from subsequent analysis.

The drainage amylase concentration increased with increasing surgical manipulation of the pancreas (*Fig. 1*). In D_2 or more extended operations with full mobilization of the pancreatic body and splenectomy, the amylase level usually exceeded 1000 (median 2517) units. The highest levels were seen in the 15 patients undergoing partial pancreatectomy.

Table 2 shows the incidence of pancreatic fistula according to the drainage amylase level on the first postoperative day. When the cut-off level is taken as 4000 units, the sensitivity, specificity and positive predictive value of the amylase concentration for pancreatic fistula development are 62, 77 and 30 per cent respectively. When the amylase level was less than 4000 units, the incidence of pancreatic fistula was 7 per cent. *Fig. 2* shows the receiver–operator characteristic curve obtained in this analysis.

The drainage amylase level on the first day exceeded 10 000 units in 13 patients. Nine of the 13 had undergone pancreas-preserving splenectomy, four of whom developed pancreatic fistula. The drainage amylase in patients who developed pancreatic fistula (median 6590 units) was significantly higher than that of those who did not (1836 units; $P < 0{\cdot}01$, Mann–Whitney *U* test).

The serum amylase level on the first postoperative day did not correlate with either the drainage amylase level or operative method, and showed no relation with the development of pancreatic fistula.

Discussion

Amylase determination in drainage fluid is often used to diagnose pancreatic fistula after pancreatic surgery[7]. Its implication in gastric surgery has not been established. The possible sources of amylase in the drainage fluid after total gastrectomy include intestinal and/or salivary amylase from leak of the oesophagojejunostomy, or secondary to postoperative acute pancreatitis. However, the lack of clinical evidence of anastomotic failure and pancreatitis in the present patients appears to render these possibilities unlikely. The most probable sources are direct leakage from the pancreatic duct after pancreatosplenectomy and seepage of pancreatic juice from the surface of the pancreas.

Drainage amylase levels clearly reflected the extent of operative manipulation of the pancreas. These results suggest that mobilization alone without pancreatectomy can damage the pancreatic parenchyma. This minor traumatic leakage, however, appears to subside spontaneously without proceeding to clinical fistula formation. In the strictest sense, not only the amylase concentration but also the volume of drainage fluid and its protein concentration should be considered because extended lymphadenectomy can lead to lymphorrhoea, possibly diluting and thereby masking pancreatic leakage. Nevertheless, simple determination of the amylase level in drainage fluid was found to be a clinically useful assessment tool.

The overall incidence of pancreatic fistula in the 102 total gastrectomy cases was 13 per cent. Among 79 patients undergoing splenectomy, the rate was 15 per cent. These values are lower than those of other series with distal pancreatectomy[8], probably because the pancreas-preserving method was employed whenever possible. Nevertheless, pancreatic fistula is not a rare complication, and close observation is mandatory. When a drain is properly placed near the pancreas, and the drainage fluid amylase level is less than 2000 units on the first postoperative day, the risk of pancreatic fistula formation is low and the drain can be removed within a few days. When the drainage fluid amylase level exceeds 4000 units, a pancreatic fistula may develop in one-third of cases, necessitating meticulous drain management. In these cases, the authors usually leave the drain in place for at least 7 days, with continuous suction if necessary, in the hope of minimizing the size of the incipient fistula. Then, when the fistula does develop, the tube is replaced and carefully adjusted under radiological guidance to achieve optimal drainage.

The role of pancreatosplenectomy in gastric cancer surgery is controversial. In the British multi-institutional trial[3], conventional and extended lymphadenectomy for gastric cancer were compared in a randomized setting. The operative mortality rate was significantly higher with extended surgery (13 *versus* 6·5 per cent), due mainly to splenectomy. The risks of splenectomy, in certain situations, exceed the possible benefits. However, there are situations in which this is not the case. The number of patients in the present series was comparable to that in the extended surgery arm of the British trial, and there were no operative deaths. This difference may be explained by four factors. First, the present patients appear to be fitter for major abdominal surgery than the British patients. Second, the pancreas was preserved in the majority of cases. Third, the present patients were operated on by a small number of specialized surgeons at a highly specialized institution. Fourth, the authors have more experience in the management of pancreatic leakage in their institution, owing to a large patient population.

In conclusion, peripancreatic lymphadenectomy with splenectomy in gastric cancer surgery is often associated with pancreatic fistula formation. Careful management of drains is essential to prevent death, and determination of the amylase content in drainage fluid on the first postoperative day may serve as a useful predictor of pancreatic fistula.

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British Association of Endocrine Surgeons Abstracts

Abstracts from the British Association of Endocrine Surgeons meeting held in Aberdeen, UK, 14–16 May 1997.

Thyroid autoimmunity is associated with favourable outcome in patients with breast cancer

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Previous reports show that asymptomatic thyroid gland enlargement and thyroid peroxidase autoantibodies (TPO.Ab) are significantly more common in women with breast carcinoma than in age-matched controls without evidence of breast disease and that the finding of either a small or a large thyroid gland is associated with a favourable outcome in patients with breast carcinoma. The aim of this study was to determine the contribution of thyroid autoimmunity as reflected by TBO.Ab status to outcome in women with breast carcinoma.

Serum TPO.Ab titres were measured in 145 women within 3 months of breast cancer diagnosis using a sensitive direct radioimmunoassay (RSR, Cardiff, UK). Women with serum titres of 0·3 units ml^{-1} or more using Medical Research Council standard 65/93 were considered TPO.Ab positive. The thyroid volume of these women was also determined using a hand-held 7·5-MHz linear ultrasound transducer to measure the width, depth and length of each lobe.

The presence of TPO.Ab was found to be associated with significantly better disease-free and overall survival. The Kaplan–Meier estimate of 5-year disease-free survival was 73 per cent for the antibody-positive patients compared with 56 per cent for the antibody-negative patients (relative risk 1·91, $P = 0{\cdot}032$; log rank test). Corresponding estimates of 5-year overall survival were 91 and 80 per cent respectively (relative risk 3·42, $P = 0{\cdot}009$). The median follow-up period was 3·45 years. The protective effect of TPO.Ab positivity was maintained in multivariate survival analysis using the Cox proportional hazards model when the prognostic effect of nodal status, tumour size, oestrogen-receptor status and thyroid volume were considered. In patient subgroups defined by thyroid volume using thresholds previously determined (9·4 and 18·8 ml), the protective effect of TPO.Ab positivity was apparent only in the group with a poor prognosis (those with an intermediate thyroid volume).

These findings suggest that thyroid autoimmunity as reflected by TPO.Ab positivity has a protective effect in patients with breast carcinoma who have an intermediate thyroid volume.

Twins with autoimmune polyglandular syndrome

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Total thyroidectomy was performed in 20-year-old twins for thyrotoxicosis as part of an autoimmune polyglandular syndrome. The presentation of the first twin was unusual. At 11 years he presented with neuropsychiatric symptoms, vomiting, dehydration and diarrhoea. No specific abnormalities were detected, apart from a low plasma sodium concentration (129 mmol l^{-1}) and he made a full recovery. Three weeks later he re-presented with similar symptoms, and he had become pigmented. The adrenocorticotrophic hormone level was raised at 2000 ng l^{-1} (10–80) and primary adrenocortical insufficiency was diagnosed by a long Synacthen test. He had a tachycardia, lid lag and diffuse enlargement of the thyroid gland; TFTs (thyroid function tests) confirmed toxicosis. Autoantibodies were detected against adrenal, gastric parietal cells, thyroglobulin and thyroid peroxidase. The second twin was subsequently examined and also found to have thyrotoxicosis and primary adrenocortical insufficiency.

Both twins were commenced on carbimazole, oral hydrocortisone and fludrocortisone, and subsequently developed huge soft vascular goitres for which total thyroidectomy was performed.

Autoimmune polyglandular syndrome type II is an uncommon condition and the combination of hyperthyroidism and adrenocortical insufficiency is rare

Epidemiology of primary hyperparathyroidism in the West Midlands

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Three years ago the authors reported an audit on parathyroidectomy during 1992 in the West Midlands which showed that 57 patients with primary hyperparathyroidism were operated on in 14 hospitals in 21 health districts by 20 surgeons Fifteen were operated on in this unit. Subsequent changes have been significant. The number of patients referred with primary hyperparathyroidism trebled between 1992 and 1996, despite the move of an endocrinologist with a special interest in calcium disorder to another hospital where patients are now operated on

More striking is the increase in the number of patients from one district (B). During 1995 and 1996 they represented 50 per cent of operated patients. District B, distant from Queen Elizabeth Hospital, does not have a specialist endocrinologist or metabolic physician. The patients are referred from a variety of doctors. It has not been targeted educationally. Review of the patients from district B shows that they have the same age range, sex ratio, and range of calcium and parathyroid hormone levels as those referred from elsewhere. The symptomatology is the same except that renal stone disease is less common in those from district B: 10 *versus* 25 per cent. The total operated on from district B in 1996 (population 300 000) made up 40 per cent of the total number of patients operated on in the West Midlands in 1992 (population 5·2 million).

If the incidence of hyperparathyroidism requiring surgical treatment is not just a local phenomenon for district B it has implications for surgical manpower planning. If this increase is reflected regionwide it equates to an eightfold increase in the need for parathyroidectomy on the 1992 figures.

Thyroid aspiration cytology

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Fine-needle aspiration cytology (FNAC) is a well established technique for the preoperative investigation of thyroid nodule(s). Thyroid FNAC was introduced in the teaching hospitals of Newcastle upon Tyne in 1981, initially with only a small group of clinicians as aspirators. Audit results for 1981–1986 inclusive showed a sensitivity of 93·5 per cent, an unsatisfactory rate of 25·3 per cent and a false-negative rate of 6·5 per cent for malignant disease. As FNAC has become more popular locally for the investigation of thyroid disease the number of clinicians performing aspiration has increased and the results for recent years have therefore been audited.

Medical records were reviewed for patients with a dominant thyroid nodule who had FNAC carried out in the 6-year period 1990–1995. Comparative analysis of cytology and histology was confined to the 239 patients who subsequently underwent partial or complete thyroidectomy.

Histology of the thyroid specimens showed 60 follicular adenomas and 34 malignant lesions (including nine follicular, 18 papillary and three medullary carcinomas). A total of 302 aspirations had been carried out on these 239 patients On cytological grounds the unsatisfactory rate was 43·7 per cent. FNAC (AC3, 4 and 5) predicted neoplasia with a sensitivity of 85·7 per cent, a specificity of 67·4 per cent, a positive predictive value of 66·7 per cent, a negative predictive value of 86·1 per cent and a false-negative rate of 14·3 per cent Malignancy was predicted with a sensitivity of 88·9 per cent and a false-negative rate of 11·1 per cent. A FNAC report of AC5 had a positive predictive value for malignancy of 100 per cent.

FNAC is an invaluable and minimally invasive procedure for the preoperative assessment of patients with a dominant thyroid nodule. It is, however, important that the number of aspirators (whether clinicians or cytopathologists) be kept small to maintain expertise and also that the results of FNAC be subject to ongoing audit.

Predictive value of intraoperative frozen section analysis of the jugulodigastric node for invasion of the lateral compartment in medullary carcinoma of the thyroid

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Conventional treatment for medullary carcinoma of the thyroid (MTC) is total thyroidectomy and cervical lymph node dissection (CLND). Central lymphadenectomy is mandatory in all patients. There is disagreement about the extent of lymphadenectomy lateral to the jugular vein. The jugulodigastric node (JDG) is a relatively constant lymph node at the apex of the central group in direct lymphatic connection with the upper pole of the thyroid. The aim of the study was to assess whether or not invasion of the JDG was predictive of invasion of the nodes of the lateral compartment.

The data of 50 sequential patients (median age 36 (range 4–73) years) considered for operative treatment for MTC were analysed retrospectively. Forty-nine operations were performed in 49 patients; 28 patients had CLND including the lateral group specifically reporting the JDG node.

Forty-six patients had invasive MTC and three had atypical hyperplasia. The primary MTC was multifocal in 21 of 34 patients in which this information was available. Nodes were involved in 27 of 47 patients.

	Lateral nodes	
	Negative	Positive
JDG negative	16	2
JDG positive	1	9

Ipsilateral intraoperative JDG node frozen section analysis predicted lateral group involvement in nine of ten patients and may be considered when planning the extent of surgery

Median sternotomy for parathyroid adenoma

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Most mediastinal parathyroid tumours lie within the thymus gland and may be retrieved when cervical thymectomy is carried out in the course of neck exploration for primary hyperparathyroidism (HPT). Infrequently, sternotomy and mediastinal exploration is required for adenoma removal.

Between October 1995 and April 1996, four patients (two men aged 49 and 42 years, two women aged 53 and 32 years) underwent sternotomy for removal of mediastinal parathyroid adenomas (weights 1·8 g, 2·0 g, 1·3 g, 480 mg) following initial unsuccessful cervical exploration. At first operation four normal parathyroid glands were identified in each of two patients, three normal parathyroids in a third, and two normal glands in the fourth; the adenoma removed from each of the first two patients therefore represented neoplastic change within a supernumerary (fifth) parathyroid gland. Following mediastinal exploration serum calcium level returned to normal in all patients. Subtraction isotope scintigraphy suggested the presence of a mediastinal parathyroid tumour before cervical exploration in two individuals and before reoperation in a third.

When localization before initial exploration for HPT suggests a parathyroid tumour within the chest, consideration should be given to proceeding to sternotomy at first operation if a comprehensive neck exploration, including cervical thymectomy, fails to uncover the adenoma.

Lifelong follow-up is necessary in phaeochromocytoma

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The recurrence of phaeochromocytoma may result from retained or implanted adrenal medullary tissue. A late recurrence can also result from the development of metastatic disease or locoregional malignant recurrence. Late recurrences of phaeochromocytoma associated with multiple endocrine neoplasia type 2 have been reported

The determination of malignancy is a particular problem in phaeochromocytoma as specific histological, biochemical or electron microscopic criteria of malignancy are absent. The diagnosis requires microscopic evidence of tumour cells in a localization where there can be no embryological residue of chromaffin tissue.

Two patients with sporadic phaeochromocytoma with late recurrence are reported. The first patient developed a malignant locoregional recurrence 13 years after undergoing complete resection of a histologically benign adrenal phaeochromocytoma. The second patient developed a hepatic metastasis 10 years after complete resection of a benign adrenal phaeochromocytoma.

Recurrence can occur in sporadic, unilateral tumours years later and lifelong follow-up is mandatory.

Variations in the surgical practice of thyroidectomy

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There is a growing trend towards specialization in all forms of surgery, and it is no longer regarded as acceptable practice for the 'general surgeon' to be undertaking small numbers of specialist surgical procedures. This may be particularly applicable in thyroid disease. To address this issue, all surgeons in the North West and Mersey regions were polled with the aim of determining their individual levels of thyroid surgical activity during the calendar year of 1995, and their 'usual practices' for certain thyroid diseases (benign and malignant).

Questionnaires were posted to 145 general surgeons, and 107 (74 per cent) were returned with analysable data. Seventy-eight (73 per cent) of 107 surgeons had undertaken some form of thyroid surgery. The median number of thyroid operations undertaken was 10 (range 1–100). The surgeons were subdivided into three groups based on their surgical activity: low activity (1–9 thyroid operations, $n=32$), intermediate activity (10–19 thyroid operations, $n=20$) and high activity (20–100 cases, $n=21$). There was some variation in the preoperative investigations undertaken by surgeons for patients with a solitary nodule All surgeons with a high level of activity used fine-needle aspiration cytology (FNAC) as a diagnostic aid, whereas only 75 per cent of low/intermediate activity surgeons used FNAC.

Likewise, surgeons in teaching hospitals were considerably more likely to use FNAC than those in district general hospitals (DGHs) (100 *versus* 80 per cent). The use of radioisotopic scanning was still used to a significant degree, by 33 per cent of teaching hospital consultants and 50 per cent of DGH consultants.

The optimal surgical management of both solitary nodules and thyroid malignancy still remains controversial. This is reflected in the practices of surgeons in the North West region: despite the logical contraindications 40 per cent of surgeons still undertake 'lumpectomy' or subtotal lobectomy for a solitary nodule. The *Table* shows the extent of resection used by surgeons in the North West for differentiated thyroid cancer; the majority of surgeons undertake total lobectomy for the involved lobe, but 21 per cent of surgeons do nothing to the contralateral lobe.

	Involved lobe			Contralateral lobe			
	Subtotal	Near total	Total	Subtotal	Near total	Total	Nothing
Papillary cancer	1	7	92	5	17	57	21
Follicular cancer	0	10	90	1	16	62	21

Values are percentage of surgeons

These data confirm heterogeneity of activity and practice in surgeons who undertake thyroid surgery and suggest the need for establishment of standards of practice and a need to encourage greater specialist involvement.

Fine-needle aspiration cytology in thyroid disease

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Fine-needle aspiration cytology (FNAC) has been advocated widely as a useful diagnostic tool in thyroid disease. The aim of this study was to critically examine the accuracy and sensitivity of FNAC in a single institution.

Between January 1990 and October 1996, 222 thyroid samples were analysed by the Department of Cytopathology. In 84 cases the patient underwent surgery, and it was thus possible to correlate cytology and histopathology in these instances. In 71 (32 per cent) of the 222 patients, the sample received by the laboratory was inadequate for a cytological diagnosis In the final study population, 30 (36 per cent) of the 84 samples were inadequate, 44 (52 per cent) were reported as benign, eight (10 per cent) were reported as follicular and two (2 per cent) were assessed as malignant. For the first analysis (analysis 1), all the 'technical failures/inadequate samples' were included in the data, assessing the global ability of the physician and the cytologist to detect malignant disease, and for the second analysis (analysis 2), these cases were excluded, thus giving a more accurate reflection of the usefulness of cytology alone, when provided with an adequate sample. The results of these analyses were

	Analysis 1	Analysis 2
Sensitivity (%)	20	100
Specificity (%)	100	91
Diagnostic accuracy (%)	90	92
False-negative rate (%)	80	0
False-positive rate (%)	0	9
Positive predictive value (%)	100	60
Negative predictive value (%)	89	100

In the 30 patients whose cytological samples were inadequate, eight malignant lesions were subsequently found by histological analysis of the resected lesion.

These data confirm that in the hands of a dedicated cytologist, FNAC is an accurate diagnostic tool, but with an important caveat: so long as the cytologist receives an adequate sample. Clearly the expertise and techniques of the person performing the aspiration can have a significant bearing on the accuracy of the technique. The most important lesson must be that an inadequate cytological sample may still hide an appreciable incidence of thyroid malignancy.

Extent of lymphadenectomy in papillary thyroid carcinoma

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The extent of lymphadenectomy at primary surgery depends on (1) the prognostic value of lymph node metastases (LNM), (2) the pattern of LNM, and (3) the existence of a surgical technique that improves survival.

There was a significant influence of LNM using univariate ($P<0\cdot00001$) and multivariate ($P<0\cdot0001$) analysis of 342 patients. Since 1986 the pattern of LNM was prospectively analysed in 35 patients undergoing microdissection. Definitions included one cervicocentral compartment (C1), two cervicolateral compartments (C2 and C3, lateral to the carotid sheath), one upper mediastinal compartment (C4, below the brachiocephalic vein) and dependency to primary tumour side as ipsilateral or contralateral.

In 24 of the 35 patients LNM were found in the ipsilateral cervicocentral compartment (pT_1 29 per cent, pT_2 67 per cent, pT_3 100 per cent, pT_4 83 per cent). LNM in the contralateral cervicocentral compartment were diagnosed only in patients with pT_3 (50 per cent) or pT_4 (25 per cent) tumours. Nineteen patients had LNM in the ipsilateral cervicolateral compartment (pT_1 57 per cent, pT_2 50 per cent, pT_3 50 per cent, pT_4 58 per cent). Contralateral cervicolateral LNM were never diagnosed. Only one patient with a pT_3 tumour had mediastinal lymph node involvement.

Surgery for papillary thyroid carcinoma should routinely include microdissection of the cervicocentral compartment and in many patients lymphadenectomy of the ipsilateral cervicolateral compartment is indicated.

Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma

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Lymph node surgery in patients with papillary thyroid carcinoma (PTC) is still controversial The benefits of prophylactic lymph node dissection (PLND) in the central neck area have not been clearly demonstrated and should be weighed against the potential risks of the procedure. The aim of the study was to assess the recurrent laryngeal nerve and parathyroid risks of PLND after total thyroidectomy in patients with PTC and to compare the results with those obtained in patients who underwent total thyroidectomy only.

One hundred patients undergoing total thyroidectomy, 50 for non-toxic benign multinodular goitre (group 1) and 50 for PTC (group 2), were studied Patients with PTC had no evidence of macroscopic lymph node invasion during surgery and underwent PLND in the central neck area in addition to the total thyroidectomy. Mean size of the PTC was 19 (range 6–60) mm Microscopic lymph node invasion was observed in 20 patients. All patients were operated on by two experienced endocrine surgeons. All patients had preoperative and postoperative investigations of vocal cord movements. Patients with a serum calcium level below 1·90 mmol l^{-1} were considered to have early postoperative hypoparathyroidism and received calcium and vitamin D therapy. The hypoparathyroidism was considered permanent when calcium and vitamin D therapy was still necessary 1 year after surgery.

	Recurrent laryngeal nerve palsy		Hypoparathyroidism	
	Transient	Permanent	Transient	Permanent
Group 1	3 (6)	0 (0)	4 (8)	0 (0)
Group 2	2 (4)	0 (0)	7 (14)	2 (4)

Values in parentheses are percentages

After total thyroidectomy for PTC, PLND in the central neck area does not increase recurrent laryngeal nerve morbidity but it is responsible for a high rate of hypoparathyroidism especially in the early postoperative course. These results make it difficult to advocate PLND as a routine procedure in the central neck area in patients with PTC.

Diagnosis and management of early hypoparathyroidism after thyroid surgery

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Hypoparathyroidism is one of the major complications of thyroid surgery. Since patients who undergo thyroidectomy are discharged early, diagnosis of hypoparathyroidism should be made shortly after surgery The purpose of this study was to determine the calcium and phosphate levels indicating early hypoparathyroidism and requiring treatment

Fifty patients were selected who underwent surgery during 1994 for papillary thyroid carcinoma which included prophylactic central neck dissection and total thyroidectomy. One hundred and sixty-seven of 200 parathyroid glands were dissected: 149 were preserved *in situ* and 18 were grafted immediately. Serum calcium (range 2·15–2·60 mmol l^{-1}) and phosphate (range 0·90–1·45 mmol l^{-1}) were measured systematically before operation, and on days 1 and 2 after surgery. Patients with a serum calcium level above 2·15 mmol l^{-1} had no further measurement (group I). Patients with levels under 1·90 mmol l^{-1} (group III) were treated immediately with oral calcium and vitamin D Patients with levels between 2·15 and 1·90 mmol l^{-1} (group II) had a third determination on day 3 When the calcium level was below 1·90 mmol l^{-1} and/or the phosphate level was above 1·45 mmol l^{-1} they were also treated In all patients parathyroid function was checked 1 year after surgery.

	Group I	Group II	Group III
No. of patients	14	27	9
Preoperative			
Calcium mmol l^{-1}	2·40	2·34	2·34
Phosphate mmol l^{-1}	0·96	1·02	1·10
Postop. day 1			
Calcium mmol l^{-1}	2·26	2·09	1·89
Phosphate mmol l^{-1}	1·10	1·19	1·31
Postop day 2			
Calcium mmol l^{-1}	2·23	2·09	1·78
Phosphate mmol l^{-1}	1·08	1·13	1·31

In groups I and II, 1 year after surgery calcium and phosphate levels were normal in all patients but four patients in group II were treated temporarily for 15–37 days. In group III, seven patients required temporary treatment for 15–90 days and two needed permanent treatment.

After total thyroidectomy there is no risk of hypoparathyroidism when serum calcium levels remain above 2·15 mmol l^{-1} on days 1 and 2. When the calcium level is below 1·90 mmol l^{-1} all patients require treatment. For patients with a calcium level between 2·15 and 1·90 mmol l^{-1} treatment is indicated when the phosphate level is above 1·45 mmol l^{-1} on day 3.

Surgical goitres in the united Bristol hospitals: 1967–1994

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In the absence of any previous study a detailed review was undertaken to (1) ascertain the volume of surgical activity; (2) record the distribution of thyroid pathology; (3) discern the pattern of surgical performance; (4) re-evaluate all examples of thyroid neoplasm; and (5) suggest a plan for future practice and training

Data were extracted from two main sources: histopathology reports, filed in volumes until 1986 and computerized thereafter; and operative surgery records for all theatres at the Bristol Royal Infirmary.

The total number of surgical goitres was 1945 (mean 69·5 per year) ranging from 114 in 1971 to 45 in 1987. There were 1200 cases of nodular goitre; 431 presented as diffuse nodularity and 284 as a solitary nodule. The rate of incidental neoplasm was 19 of 1200 (2 per cent). Neoplasms are subject to review but, considering malignancy, there were 166 new patients, leading to 184 annual patient entries, resulting in 191 operations (53 per cent for papillary carcinoma), a mean of 6·8 per year Some 202 patients had follicular adenoma; 30 adenomas (15 per cent) developed within chronic lymphocytic thyroiditis (CLT). Of the 129 patients requiring surgery for CLT, only 48 (37 per cent) had the 'classical' diffuse form. Throughout the 28 years, there were persistent examples of general surgeons dealing with one or two patients per year.

It is concluded that one or perhaps two surgeons with a devoted endocrine commitment could manage surgical goitres, especially the neoplasms, from this location and provide a comprehensive training.

Intraoperative parathyroid hormone level during surgery for primary hyperparathyroidism

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Parathyroid hormone (PTH) was measured at operation in 119 patients during 121 operations for primary hyperparathyroidism (HPT). The preoperative mean(s.d.) serum calcium level was 2·79(0·21) mmol l^{-1}. Fourteen patients had previous neck surgery. Blood samples were drawn before, and 5 and 15 min after excision of the first enlarged parathyroid gland. PTH was analysed electively in 71 patients and on-line by a modified assay for intact PTH in 58 patients.

The mean(s.d.) decline in PTH level in 101 patients with primary exploration because of solitary adenoma was 63(17) per cent after 5 min ($n = 84$) and 83(10) per cent after 15 min. The patients with primary exploration because of multiglandular disease ($n = 6$) were correctly predicted not to have parathyroid adenoma by the decrease in PTH level. On-line monitoring of the decrease in PTH level was helpful in guiding the amount of parathyroid tissue to be resected in patients with previous neck surgery.

The measurement of PTH level during surgery for primary HPT is a highly sensitive method to differentiate between single and multiple gland disease. The on-line measurement is clinically useful in patients with previous neck surgery. Its role in primary HPT surgery before primary exploration should be evaluated in prospective trials.

Severe amiodarone-associated thyrotoxicosis is a surgical emergency

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Amiodarone-associated hyperthyroidism has been reported as mild with thyroid function returning to normal after discontinuation of the drug and/or under medical therapy. Severe life-threatening amiodarone-associated thyrotoxicosis (AAT) has also been described. In such extreme cases conventional conservative treatments are essentially ineffective or fail to alter the dramatic course of thyroid crisis and thyroidectomy is indicated.

Fifteen patients (12 men and three women of mean age 68 years) were studied and six underwent total or near-total thyroidectomy, as first line therapy. Duration of amiodarone treatment before diagnosis ranged from 1 day to more than 48 months. Severe AAT developed unpredictably and most often suddenly. Surgery was indicated on the basis of a very rapid deterioration of general condition (weight loss more than 10–15 per cent of the total body mass over a few weeks) and relapse and worsening of cardiac arrhythmias associated with severe cardiac failure. Two patients requiring intensive care were considered as terminal at the time of surgery. The most critically affected patients exhibited very high levels of reverse T3 (more than 150 ng ml^{-1}; normal value 15–35 ng ml^{-1}).

Surgery resulted in a spectacular and almost immediate resolution of thyrotoxicosis. Rapid and continuous significant cardiac improvement was noted. No thyroid storm was observed. General anaesthesia, surgery and immediate recovery were uneventful.

It is no longer acceptable to persist with conservative medical treatment when AAT becomes severe and life threatening. Surgery is the best option, even in the elderly, frail and thyrotoxic patient. This treatment permits the continuation of amiodarone when the drug is considered as unique in managing the underlying cardiac arrhythmia.

Endocrine surgery under hypnosis: from fiction to daily clinical use

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This study examined the hypothesis that hypnoanaesthesia could provide benefits in cervical endocrine surgery, making easier the physical and/or psychological recovery of patients after this type of surgery.

Between April 1994 and March 1996, 108 thyroidectomies (97 partial or unilateral lobectomies and 11 bilateral lobectomies) and 13 cervical explorations for hyperparathyroidism were performed under hypnosedation (HS) according to the Milton Erickson's method. Informed consent was obtained from each patient. No patient underwent preoperative standard susceptibility tests or a preparatory hypnotic session. Operative data and postoperative courses were compared with those of a well matched population ($n = 70$) of patients operated on under general anaesthesia (GA).

Under HS, no patient required conversion to GA. The mortality rate was zero. One patient suffered unilateral definitive recurrent laryngeal nerve paralysis and another needed neck re-exploration for severe haematoma after parathyroidectomy. Hyperparathyroidism was cured in all cases. The surgeons reported better operating conditions as estimated by visual analogue scale (VAS) using HS (mean(s.d.) 8·9(0·6) *versus* 8·0(1·2) cm in the GA group, $P < 0{\cdot}01$). This is probably related to the hypnotic effect on blood flow, reducing local bleeding. All patients reported a very pleasant experience and enjoyed having their surgery performed under HS (VAS of satisfaction 9·3(1·0) *versus* 2·9(2·8) cm in the GA group, $P < 0{\cdot}001$). Patients having HS had less postoperative pain (VAS 2·2(1·6) *versus* 3·2(2·0) cm in the GA group, $P < 0{\cdot}01$), and the requirement for analgesic drugs was significantly reduced in comparison with that of the GA group (mean(s.d.) paracetamol on day 1: 932(519) *versus* 1437(622) mg in the GA group, $P < 0{\cdot}001$). Hospital stay was significantly shorter (mean(s.d.) 46·3(14·6) *versus* 74·2(9·5) h in the GA group, $P < 0{\cdot}001$), providing a substantial reduction in medical costs. The postoperative fatigue syndrome and convalescence were significantly improved after HS (VAS of fatigue 2·0(2·0) *versus* 4·7(2·4) cm in the GA group, $P < 0{\cdot}001$; hand grip test. 95·5 per cent of preoperative muscular maximum force *versus* 89·9 per cent in the GA group, $P < 0{\cdot}01$) Full return to social or professional activity was accomplished after mean(s.d.) 10·3(10·2) days in the HS group *versus* 36(8) days in the GA group ($P < 0{\cdot}001$).

HS is a very effective method, providing relief of intra-operative and postoperative pain in cervical endocrine surgery. This technique results in high patient satisfaction and a quicker convalescence; it can therefore be used for most patients and reduces the socio-economic impact of hospitalization.

Requirement for drains in thyroid surgery

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Systematic drainage in thyroid surgery is a routine but empirical tradition with no scientific evidence to support it. A retrospective review of a personal series of 1789 thyroidectomies over a 3·5-year period was performed to examine this question.

Except for thyroid cancer surgery with lymphadenectomy and large mediastinal goitres requiring sternotomy, no case selection for drainage or no drainage was employed. Patients were stratified on a chronological basis only, according to the fact they were drained ($n = 575$, 1993–1994) or not ($n = 1214$, 1994–1996). Both series included toxic goitres, large endothoracic compressive goitres, bilateral and redo procedures.

Severe life-threatening haematoma requiring re-exploration occurred in five patients who had drains (0·9 per cent) and in five patients who did not undergo drainage (0·4 per cent). Minor postoperative wound haematomas were treated conservatively in 17 patients with drains (2·9 per cent) and six without (0·5 per cent).

	Drainage ($n = 575$)	No drainage ($n = 1214$)	Total ($n = 1789$)
Minor haematoma	17 (2·9)	6 (0·5)*	23 (1·3)
Life-threatening haematoma	5 (0·9)	5 (0·4)	10 (0·6)
Total	22 (3·8)	11 (0·9)*	33 (1·8)

*$P < 0{\cdot}001$

Drainage after thyroid surgery is not mandatory provided that the field is completely bloodless before closure. There has been progressive change in the operative technique which now includes ligature and suture of anterior jugular veins, no section of the strap muscles, minimal use of electrocautery, extensive use of ultraligatures and titanium clips, and packing of the dead space with cellulose swabs

Apoptosis in thyroid diseases

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Apoptosis is a form of cell death distinct from necrosis and characterized by nuclear segmentation, cytoplasmic condensation, membrane blebbing and endonuclease-induced fragmentation of DNA. This study was designed to quantify the degree of apoptosis in Graves' disease ($n=8$), Hashimoto's thyroiditis ($n=4$) multinodular goitre ($n=5$) and normal thyroid tissue ($n=1$), by *in situ* immunofluorescence (Tunel).

The susceptibility of thyrocytes and infiltrating lymphocytes to apoptosis was determined by the expression of *bcl2*, a proto-oncogene with an antiapoptotic effect, and APO-1/FAS which induces cell death by cross-linkage of a transmembrane protein related to the tumour necrosis factor receptor family. Monoclonal antibodies to both *bcl2* and APO-1/FAS molecules were applied to an immunocytochemistry assay on thyroid cryostat sections.

An increased level of apoptosis was detected in Hashimoto's glands both by flow cytometry and *in situ* techniques in comparison with findings in Graves' disease and non-autoimmune glands. The findings in Hashimoto's thyroiditis were associated with a decreased *bcl2* staining and a *de novo* patchy APO-1/FAS reactivity on thyrocytes

The dysregulation of apoptosis-related genes may be a major aetiological factor in the programming of destructive thyroid autoimmunity and the locally produced cytokines may be responsible for this dysregulation.

Prospective management protocol for cystic lesions of the thyroid

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Although mostly benign, fluid-containing lesions of the thyroid can be malignant. This study examined this risk and defined predictive groups.

Between 1990 and 1995, 186 cystic lesions of the thyroid were diagnosed from 1041 new patients (61 with cancers) These lesions were classified into three groups to determine management: (1) Focal thyroid masses which became impalpable following up to three aspirations of more than 0·5 ml were treated conservatively provided there were no other indications for surgery. (2) Thyroidectomy was advised for cystic masses which either persisted or recurred after aspiration. (3) All other documented cystic lesions (e.g. found on ultrasonography in a multinodular goitre) were treated on their merits.

Most patients (88 per cent) underwent ultrasonography. Some 137 lesions (74 per cent) were aspirated and cytology was requested in 69 (37 per cent), 32 per cent of these being inadequate specimens. Of 61 cancers, six (10 per cent) had a cystic component. Only three of these cystic cancers underwent cytological analysis and all were positive; however, results for five of 38 benign lesions were falsely positive. No unsuspected malignancies have been detected on follow-up.

	Group 1 ($n=60$)	Group 2 ($n=56$)	Group 3 ($n=70$)
Median (range) age (years)	40 (17–83)	40 (14–83)	47 (15–71)†
Nature of lesion			
Benign/hyperplastic	8	24	19
Other benign	4	9	4
Cancer	0	6†	0
No operation*	48 (80)	17 (30)	47 (67)

*Values in parentheses are percentages †$P<0·05$

It is concluded that approximately 3 per cent of cystic lesions of the thyroid are malignant, but risk groups can be defined

Survival after surgery for malignant endocrine pancreatic tumours

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All patients with malignant endocrine pancreatic tumours (EPT) surgically explored at Sahlgrenska hospital between 1981 and 1996 were studied. Twenty-five patients had sporadic tumours (five insulinomas, five gastrinomas, three neuroendocrine carcinomas, two pancreatic carcinoids, two glucagonomas and eight non-functional tumours) and ten had multiple endocrine neoplasia (MEN) one syndrome and gross tumours (seven insulinomas, two gastrinomas and one PPoma (endocrine pancreatic tumour with main production of Pancreatic Polypeptide))

The 5-year survival rate for patients with sporadic lesions (age 25–87 (mean 47) years) was 47 per cent; of these patients 13 had resection with curative intent, with a 5-year survival rate of 92 per cent (mean follow-up 53 months). The disease recurred in three of 12 patients after 33–88 months Twelve patients underwent palliative surgery followed by hepatic arterial embolization and/or chemotherapy. The 2- and 5-year survival rates were 60 and 0 per cent respectively.

The 5-year survival rate for the patients with MEN-1 (age 29–68 (mean 41) years) was 90 per cent; of these patients nine had curative resection, with a 5-year survival rate of 100 per cent (mean follow-up 147 months). The only symptomatic patient underwent palliative surgery and died after 4 years.

It can be concluded that (1) intentionally curative surgery in EPT prolongs survival, although the disease will recur in most patients; (2) debulking surgery may be of benefit in patients with severe hormonal symptoms but probably adds little to survival; and (3) the favourable prognosis in patients with MEN-1 may result from both active surgical treatment and different tumour biology

Lobectomy as surgical treatment for patients in low-risk categories with differentiated thyroid cancer

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There are conflicting views on the role of surgery in the management of differentiated thyroid cancer (DTC) between routine total thyroidectomy, often as two staged lobectomies, and unilateral lobectomy alone. The situation is confused by the variable behaviour of DTC with a minority of patients falling into a low-risk category with an intrinsically good prognosis regardless of the extent of surgical therapy Furthermore, most of the data on outcome derive from specialist centres with referral patterns which may not apply to services providing thyroid surgery to a population

The outcome of a consistent policy of conservative surgery for DTC in a population of approximately 500 000 over a period of 20 years is reported. Some 248 patients (122 papillary, 83 follicular, 13 medullary, seven anaplastic, 13 lymphoma and 11 metastatic lesions) undergoing surgery for thyroid cancer were followed in a dedicated clinic. TSH suppression was routine

Of the 205 patients with either papillary or follicular carcinoma 55 underwent bilateral surgery, either total thyroidectomy or total lobectomy with subtotal lobectomy for bilateral or advanced disease Some 147 patients underwent lobectomy alone; in 38 involved lymph nodes were also excised and in 27 there was extrathyroidal spread. Four patients underwent subsequent contralateral lobectomy, two for disease in the contralateral lobe and two for a rising thyroglobulin level, but the resected lobe showed only chronic lymphocytic thyroiditis.

These preliminary data suggest that a selective policy of conservative surgery for low-risk patients with unilateral disease is associated with a low rate of subsequent completion total thyroidectomy.

Late outcome of 304 consecutive patients with multiple gland enlargement in primary hyperparathyroidism treated by conservative surgery

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The late outcome of patients with primary hyperparathyroidism (HPT) and multiple gland enlargement (MGE) treated by conservative surgery was assessed. MGE in primary HPT is defined as the presence of two or more enlarged glands weighing more than 50 mg. Conservative surgery involves resection of the grossly enlarged glands without biopsy of the normal glands. Some have suggested that this might overlook hyperplasia, leading to late recurrence of HPT or, conversely, result in the unnecessary resection of grossly enlarged, but not hyperfunctioning glands.

Some 1221 patients were operated on for HPT between 1966 and 1955; 304 (25 per cent) had MGE, including 42 (14 per cent) with multiple endocrine neoplasia (MEN), 12 (4 per cent) with familial disease and 250 (82 per cent) with sporadic disease. Two, three or four glands (or more) were involved in 62, 21 and 16 per cent of patients respectively. In the early postoperative period, one patient died and ten had to be reoperated for persistent hypercalcaemia. The pathological diagnosis was double adenoma in 13 per cent, hyperplasia in 36 per cent, adenoma associated with hyperplasia in 40 per cent and a normal second gland in 20 per cent.

Some 190 patients were available for follow-up (mean 89·3 months); 90 per cent are normocalcaemic (calcium level between 2·2 and 2·6 mmol l^{-1}), 5 per cent hypocalcaemic and 5 per cent hypercalcaemic. A total of 147 had a late i.PTH assay. The PTH level was appropriate to serum calcium in 84 per cent and appropriate to normal serum calcium level in 92 per cent of 132 normocalcaemic patients. None of the 30 deaths that occurred during follow-up was related to HPT.

Conservative surgery is an acceptable treatment for MGE in HPT. Few late recurrences occur, for which there are no individual predictive criteria.

Variable expression of fibroblast growth factors in parathyroid disease

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The expression of fibroblast growth factor (FGF) receptors in parathyroid tissues has been reported previously. This study examined the expression of FGFs 1, 2, 3 and 7 in parathyroid adenomas ($n = 10$), hyperplastic parathyroid tissue ($n = 10$) obtained from patients with chronic renal failure and in normal parathyroid tissues ($n = 4$), using reverse transcription polymerase chain reaction (RT–PCR).

FGFs 1 and 2 were expressed in most samples at variable levels, with no correlation between disease type and amplified RT–PCR product levels. FGF7 was expressed in normal parathyroid tissue and single adenomas but was absent in all but one of the renal samples. FGF3 was variably expressed in diseased tissue, in some instances at high levels.

The presence of FGF 1 and 2 transcripts in most of the samples suggests that this class of growth factor has a role in parathyroid growth processes. The lack of FGF7 expression in renal parathyroid samples compared with normal and adenomatous tissue implies that there is variation in the involvement of FGFs in different disease states that requires further investigation. The presence of raised levels of FGF3 expression in abnormal parathyroid tissue may be significant since the FGF3 gene (the *int2* proto-oncogene) is located on chromosome 11q13·3, a region susceptible to rearrangement/mutation in parathyroid disease.

Role of magnetic resonance imaging in preoperative assessment in patients with hyperparathyroidism

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The need for preoperative localization in patients undergoing the first operation for hyperparathyroidism (HPT) is disputed and current techniques are not generally considered sufficiently sensitive or specific to justify the additional cost for routine use. Although a case has been made for magnetic resonance imaging (MRI) before re-exploration, there has been only one critical assessment of its usefulness before a first operation. The aim of this study was to assess prospectively the value of MRI in the preoperative localization of abnormal parathyroid glands in patients undergoing surgery for HPT.

A group of 17 patients (12 with primary HPT; five with HPT secondary to renal disease) undergoing a first operation agreed to undergo MRI before surgery. Transverse T1- and T2-weighted scans and coronal STIR scans were obtained using a Siemens Magnetom Impact scanner to identify abnormal parathyroid tissue. The results of scans were not disclosed before surgery, the operation findings, pathology and gland weights were compared retrospectively with the MRI images.

At operation 67 glands were identified in 17 patients; 32 were deemed abnormal and were removed. Five patients underwent total parathyroidectomy for HPT associated with chronic renal failure. Twelve patients underwent excision of one or two glands for presumed adenomatous disease. The median weight of the removed parathyroid glands was 468 (range 68–19000, mean 777) mg. MRI detected 14 of the 32 abnormal glands and correlated with the size of the gland; glands weighing less than 450 mg were not detected. There were four false-positive results on the scan, two related to abnormal thyroid tissue. The sensitivity of MRI was low at 44 per cent. All patients were rendered normocalcaemic.

It is concluded that MRI is not a useful adjunct to surgery for HPT in which surgery alone achieves a success rate of over 98 per cent.

Parathyroidectomy for primary hyperparathyroidism leads to a reduction in markers of bone resorption by 24 hours

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Parathyroid hormone (PTH) stimulates osteoclast activity leading to an increase in bone resorption. Successful parathyroid surgery may reverse the increase in bone resorption observed in patients with primary hyperparathyroidism (HPT). Although PTH levels fall within 15 min of parathyroidectomy, the immediate effects on bone turnover are unknown.

Serum markers of bone formation (bone-specific alkaline phosphatase) and resorption (tartrate-resistant acid phosphatase; TRAP), and urinary markers of resorption pyridinoline (Pyr) and deoxypyridinoline (Dpyr) were measured in eight patients with HPT (mean serum calcium 2·74 mmol l^{-1}) before surgery and within 24 h of excision of a single parathyroid adenoma. Five age- and sex-matched controls undergoing surgery were also studied.

Preoperative values of serum markers of bone turnover were not significantly different between patients and controls. In both groups, there were no significant changes in markers of bone formation at 24 h. In the patient group, all markers of bone resorption fell significantly by 24 h ($P<0{\cdot}02$, Wilcoxon rank test) (*Table*).

	Serum TRAP	Urinary Pyr	Urinary Dpyr
Median percentage decrease at 24 h	18 (7–41)	22 (7–40)	35 (9–46)
P	<0·02	<0·02	<0·02

Values in parentheses are ranges

In patients with HPT, PTH stimulates bone resorption. Parathyroidectomy leads to a fall in markers of bone resorption by 24 h but markers of bone formation do not change acutely.

Decreased expression of calcium receptor messenger RNA in sporadic parathyroid adenomas

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Secretion of parathyroid hormone is regulated by extracellular calcium via calcium receptors (CaR) on the parathyroid cell surface. Pathological parathyroid glands have an increased set-point, i.e. a lowered sensitivity to calcium. The expression of CaR messenger RNA (mRNA) in sporadic parathyroid adenomas was studied using *in situ* hybridization techniques.

Operative specimens (pairs of adenomas and biopsies of adenoma-associated normal glands; and biopsies of normal glands from patients with thyroid disorders) were snap-frozen in liquid nitrogen and stored at −70° until analysis. Cryostat sections (14 µm) were hybridized with an oligonucleotide complementary to the extracellular domain of the CaR mRNA. A sense probe was used as negative control. After hybridization and rinsing, the sections were air dried and exposed to radiographic film for semiquantification of radioactivity.

Clinical data and hybridization results from patients with adenoma ($n=17$) are shown in the *Table*.

Age (years)	Serum calcium (mmol l^{-1})	Serum parathyroid hormone (ng l^{-1})	Adenoma weight (mg)	CaR mRNA in adenoma (% of normal)
72 (43–84)	2·78 (2·61–2·96)	100 (61–234)	730 (125–2900)	64 (41–98)

Values are median (range)

CaR mRNA in biopsies from adenoma-associated normal parathyroid glands was not different from that of parathyroids ($n=4$) from normocalcaemic subjects with thyroid disease: mean(s.d.) 1551(289) and 1627(100) nCi g^{-1} respectively.

It is concluded that lowered levels of CaR mRNA in parathyroid adenomas may contribute to the increased set-point of parathyroid hormone secretion seen in patients with hyperparathyroidism.

Expression of *bcl2* and *bax* proto-oncogenes detected by immunocytochemistry in parathyroid adenomas

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The low growth rate and values of proliferative markers (e.g. Ki67) in parathyroid adenomas supports the hypothesis that by the time of surgical treatment the proliferation rate of parathyroid adenoma cells has been inhibited by hypercalcaemia. As the balance between proliferation and apoptosis determines tumour progression, this study examined the expression of *bcl2* and *bax* (two related proto-oncogenes known to modulate progression through the apoptotic pathway) in glands from patients with primary hyperparathyroidism (HPT).

A standard immunoperoxidase technique was used to evaluate *blc2* and *bax* expression in 47 parathyroid adenomas, one carcinoma and eight biopsies of normal glands from patients with primary HPT. The slides were analysed by two independent observers and the intensity of the staining evaluated on a five-point scale as weak (score 1), moderate (2–3) or strong (4–5).

Homogeneous cytoplasmic *bcl2* immunostaining was demonstrated in 45 of 48 parathyroid tumours; *bax* immunostaining appeared less intense (21 of 48 tumours being classified as negative or weak) and with granular intracellular distribution. Seven biopsies had more intense *bcl2* immunostaining than the corresponding adenomas (mean score 1·2 *versus* 3·0, $P<0{\cdot}05$) while *bax* immunostaining showed an inverse correlation (mean score 0·6 *versus* 2·5, $P<0{\cdot}05$ ($n=4$)). The *Table* shows the cross-correlation of *bcl2* and *bax* immunostaining in parathyroid tumours.

	bcl2 expression				
	Negative	Weak	Moderate	Strong	Total
bax					
Negative	1		3	2	6
Weak		5	9	1	15
Moderate	2	1	22	1	26
Strong			1		1
Total	3	6	35	4	48

$\chi^2=7{\cdot}99$, $P<0{\cdot}05$

These data are the first to demonstrate the expression of *bcl2* and *bax* in parathyroid glands. As *bcl2* protects epithelial cells from entering apoptosis while *bax* has a 'pro-apoptotic' effect, the predominance of *bcl2* expression over *bax* expression in parathyroid tumours will induce a cell death protective effect. The enhanced *bcl2* expression in the biopsies of normal glands from patients with primary HPT may represent a survival mechanism in a high-calcium environment.

High cytoplasmic calcium ion concentration enhances *bcl2* expression in human parathyroid cells

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In primary hyperparathyroidism (HPT) abnormalities in the calcium-sensing mechanism (e.g. reduced expression and/or function of the calcium receptor) in tumoral parathyroid cells allow uninhibited parathyroid hormone secretion in the face of a high plasma calcium concentration. The effect of abnormal calcium sensitivity on parathyroid cell proliferation is not clearly understood. The authors have found that parathyroid adenomas have high levels of expression of *bcl2*, a proto-oncogene which protects epithelial cells from entering apoptosis. The aim of this study was to evaluate factors modulating *bcl2* expression in human parathyroid cells.

Parathyroid adenoma cells from patients with primary HPT ($n=7$) were dispersed and maintained in primary culture in RPMI-1640 medium. Fluorescent microscopy of Fura2/AM-loaded cells was used to demonstrate that the calcium ionophore A23187 and thapsigargin induce a dose-dependent and sustained rise in cytoplasmic calcium ([Ca^{2+}]$_i$). Both these drugs can induce apoptosis in many types of cell. When parathyroid cells were incubated for 48 h with A23187 (1–10 μmol l^{-1}) or thapsigargin (0·5–3 μmol l^{-1}), no significant change in cell number was identified using direct cell count or the MTT assay (quantification of viable cells by a colorimetric assay based on their ability to convert MTT, a soluble tetrazolium salt). Cytospins of cultured cells were immunostained for *bcl2* expression by a standard immunoperoxidase technique. Two independent observers, blinded to the incubation protocol used, evaluated the intensity of the staining from 1 (weak) to 3 (strong) for an average of 400 cells per slide, and an overall score was calculated. The mean(s.d.) score for staining intensity was significantly higher for cells incubated with thapsigargin (185·6(12·4)) and A23187 (187·5(10·8)) compared with controls (142·7(14·5)) ($P<0·001$, χ^2 test).

These data suggest that *bcl2* expression in human parathyroid cells is enhanced by increased $[Ca^{2+}]_i$. Since both thapsigargin and A23187 failed to increase the rate of apoptosis in parathyroid cells, the results suggest that induction of *bcl2* expression by high $[Ca^{2+}]_i$ might be a protective mechanism for parathyroid cells. In primary HPT this survival mechanism could be significant for normal parathyroid cells (whose $[Ca^{2+}]_i$ is higher than that of adenoma cells)

Somatic mutations of *ret* proto-oncogene in patients with sporadic medullary thyroid carcinoma

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Germline mutations of the *ret* proto-oncogene are the underlying genetic event in patients with familial medullary thyroid carcinoma (FMTC). The aim of this study was to verify if the same mutations are also involved in the oncogenesis of sporadic MTC (sMTC).

DNA was extracted from frozen tumour tissue and from blood samples of 23 patients with sMTC. A genomic amplification encompassing exons 10, 11, 13, 14 and 16 of the *ret* proto-oncogene was created by polymerase chain reaction (PCR) and the appropriate primers. The PCR amplified fragments were purified and treated with restriction endonucleases. After separation by polyacrylamide gel electrophoresis, cloned DNA was sequenced and resolved in 6 per cent denaturing polyacrylamide gels.

No blood sample contained *ret* mutations. In eight of 23 tumours *ret* mutations in codon 918, exon 16, leading to a methionine to threonine change were detectable.

Somatic *ret* mutations are present in a significant number of sMTCs. In this study exclusively Met918Thr mutations were found. The diagnosis of an apparently sMTC can be confirmed by presence of somatic *ret* mutations. The prognostic value of the *ret* mutations in sMTC is still unclear.

Surgical treatment of childhood thyrotoxicosis

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Thyrotoxicosis in childhood is rare, and experience in its management is limited. The role of surgery is ill defined and there is little to guide the surgeon on the management of this condition.

A paediatric endocrine clinic was established in 1973, and all patients treated at the clinic were reviewed. The clinic made regular visits to regional hospitals, at which some patients received all their treatment.

Eighty-four patients were treated for established thyrotoxicosis. Of these, eight had incomplete records and four were lost to follow-up, leaving 72 children for analysis. All patients were treated with antithyroid drugs (ATD) in the first instance. While 18 patients remain on ATD, 34 had a remission and 20 had no remission, 16 being treated surgically and four by radioactive iodine. Following initial remission, 20 patients relapsed; six responded to ATD, three remain on ATD, one had iodine therapy and ten had surgery. Of the 26 patients who had an operation there was one complication (hypoparathyroidism) and one case of recurrent thyrotoxicosis treated by iodine. Patients treated by total thyroidectomy and immediate replacement therapy proved easiest to manage.

Surgery, either total or near-total, proved safe and effective management restoring normality more quickly than therapy with ATD or iodine. A total thyroidectomy appeared to be the procedure of choice.

British Journal of Surgery 1997, 84, 1322–1323

Correspondence

Management of ileosigmoid knotting

Sir
This article by Dr Akgun (*Br J Surg* 1977; 84: 672–3) was interesting. Volvulus in adults is relatively rare in the western world[1] but lessons learned may be extrapolated to bowel surgery in general. My comments concern primary resection and anastomosis in patients with volvulus of the large bowel.

In North Western Pakistan, in 1 year, 27 patients underwent operation in our department after failed conservative treatment. Primary anastomosis was used whenever possible as our incidence of recurrence with other techniques was unacceptably high. Eight patients had a gangrenous sigmoid colon. There was no correlation between age or duration of symptoms and the incidence of gangrene. Patients presented at intervals of 12 h to 7 days. All patients presenting after 3 days had viable colon. At operation, bowel contents were evacuated but colonic lavage was not used. The outcome in these patients is summarized in *Table 1*.

Table 1 Outcome of operation in 27 patients with sigmoid volvulus

	Post-operative toxicity (major and minor)	Gangrenous bowel	Hospital stay (days)	Mortality
Primary resection and anastomosis (19)	7	4	7·0	1*
Other surgical procedures (8) (Hartmann's procedure, operative detorsion and mesosigmoid plication)	6	4	8·5	1†
Total	13	8		2

*Gangrene extending to the lower rectum on relaparotomy; †faecal peritonitis

Three patterns of gangrene were observed. Patchy gangrene (one), total sigmoid gangrene (five) and gangrene extending to the rectum (two). The patients with gangrene extending to the upper rectum had the superior rectal artery involved in the torsion. The factors associated with postoperative toxicity were faecal soiling due to perforation or surgery and any episode of systemic hypotension. Splanchnic vasoconstriction leading to colonic hypoxia and inadequate healing at the anastomosis seem to be important in this setting. Most of the patients (25) had had previous episodes of volvulus. In these patients the sigmoid colon was thickened and the mesentery fibrosed. There was perivascular fibrosis on histology. This may have been beneficial in delaying the onset of gangrene. Primary anastomosis may be safer in this scenario because of the 'protected' state of the colonic vasculature.

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1 Botsford TW, Healey SJ, Vaith F. Volvulus of colon. *Am J Surg* 1968; 114: 900–3.

Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: an audit of 5913 cases

Sir
We enjoyed reading the audit of laparoscopic cholecystectomy and bile duct injury from the West of Scotland group (*Br J Surg* 1996; 83: 1356–60) and the subsequent correspondence related to the article (*Br J Surg* 1997; 84: 730–1).

We support the view expressed by Mr Fullerton that bile duct injury during laparoscopic cholecystectomy is not avoided by operative cholangiography and would suggest that there is no conclusive evidence that cholangiography leads to a decreased incidence of duct injury[1]. In the era of open cholecystectomy and routine intraoperative cholangiography (IOC), it was shown that almost one-half of the duct injuries at cholecystectomy were caused before the performance of IOC[2] and cholangiography itself could cause duct injury[3,4]. The real problem with IOC is that it is too often used instead of careful and painstaking dissection.

There is no doubt that careful identification of the anatomy, particularly in Calot's triangle, before clipping of the cystic artery and duct, combined with a low threshold to convert to open cholecystectomy should reduce iatrogenic bile duct injury and it is this message that needs to be imparted to trainees.

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1 Macintyre IMC, Wilson RG. Laparoscopic cholecystectomy. *Br J Surg* 1993; 80: 552–9.
2 Andren-Sandberg A, Alinder G, Bengmark S. Accidental lesions of the common bile duct at cholecystectomy. Pre- and perioperative factors of importance. *Ann Surg* 1985; 201: 328–32.
3 White TT, Hart MJ. Cholangiography and small duct injury. *Am J Surg* 1985; 149: 640–3.
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Delay in treatment for oesophageal cancer

Sir
Definitive diagnosis of oesophageal cancer often occurs at a disappointingly late stage. Mr Rothwell and colleagues (*Br J Surg* 1997; 84: 690–3) identified a number of causes of delay including delay in appointments for oesophagogastroduodenoscopy, barium swallow or outpatient clinics. Delays in hospital diagnosis will be reduced by the general practitioner (GP) making a direct referral by facsimile or telephone to the consultant endoscopist for urgent endoscopy.

Examining data on the last 25 patients referred in this manner with dysphagia due to oesophageal cancer, the median (range) time from GP referral to endoscopy and biopsy was 17 (0–180) days. Two patients had lengthy delays because of treatment in other departments (160 and 180 days) and if these are excluded, the median was 13 days.

As Rothwell *et al.* state, dysphagia is a 'specific symptom' for oesophageal cancer. These patients should bypass the outpatient and radiology waiting lists and proceed directly to a consultant endoscopy list where diagnosis can be made and treatment initiated.

We believe that 'open access' endoscopy lists have little to offer in facilitating diagnosis in these patients as suggested recently by Martin *et al*[1] as this approach may lead to more endoscopies being performed without benefit[2].

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1 Martin I, Young S, Sue-Ling H, Johnston D. Delays in the diagnosis of oesophagogastric cancer: a consecutive case series *BMJ* 1997; **314**: 467–70
2 Holdstock G, Wiseman M, Loehry C. Open-access endoscopy service for general practitioners. *BMJ* 1979; 1: 457–9.

Single-visit venous ulcer assessment clinic: the first year

Sir
Mr Scriven and colleagues have demonstrated the accuracy and feasibility of determining ulcer aetiology in specialized single-visit clinics for patients with leg ulcers (*Br J Surg* 1997, **84**: 334–6). We agree that ulcers are traditionally assessed poorly in the community and a study in East Gloucestershire showed that 74 per cent did not have a clearly defined aetiology – a 'precarious' nursing management practice[1]. We believe accurate and objective assessment is essential in the rational, long term management of all leg ulcers and in 1995 established a specialized community-based leg ulcer service with a similar initial non-invasive vascular assessment to help in the management of these patients[2]. The duplex findings were similar to those reported by Scrivens *et al.*, confirming a high proportion of ulcerated limbs with superficial vein disease alone (52 per cent), a pattern of reflux amenable to surgery. All patients with superficial venous reflux alone were encouraged to have superficial vein surgery and were reviewed regularly. The results to date have failed to show a significant improvement in healing rates between limbs treated with four-layer compression and surgery (54) and those treated with four-layer compression alone (22). This comparison, however, is a non-randomized study with a median time from presentation to surgery of 6 weeks. A significant reduction in 1-year recurrence rates was demonstrated (8 *versus* 37 per cent, $P < 0.01$, Kaplan-Meier, log rank test) confirming that prevention of recurrence, rather than improvement in healing (as suggested by Scriven *et al.*) may be the clinical endpoint that justifies the use of routine duplex in all such patients in the community.

A small percentage of ulcerated limbs heal poorly despite surgery and this may be due to other problems such as immobility, calf muscle wasting, limb paralysis, obesity or fixation of the ankle joint. It may be possible to identify some of these patients at the outset with a simple calf pump power assessment such as that obtained with the portable digital-photoplethysmography unit. This measures calf muscle and joint activity, the 'percentage venous pump power' being the maximum blood displacement achieved by muscle pump action.

There is clearly a need for a randomized controlled trial in the community with sufficient follow-up to look at the effect and cost benefit of superficial vein surgery on healing and recurrence of ulcerated limbs, including those with deep vein reflux. Our results in a non-randomized group confirm the long-term benefit of accurate assessment and support the use of routine duplex in all patients to identify those amenable to surgery.

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1 Husband LL. The management of the client with a leg ulcer: precarious nursing practice. *J Adv Nurs* 1996; 24: 53–9.
2 Grabs AJ, Wakely MC, Nyamekye I, Ghauri ASK, Poskitt KR. Colour duplex ultrasonography in the rational management of chronic venous leg ulcers. *Br J Surg* 1996; 83: 1380–2.

Authors' reply

Sir
We thank Messrs Ghauri and Poskitt for their interest and comments. With the advent of duplex scanning the anatomical distribution of venous reflux in ulcerated limbs is becoming more readily and accurately apparent and over 50 per cent of such limbs have isolated saphenous venous reflux that is easily treatable surgically. We find it interesting that Ghauri and Poskitt have not demonstrated any advantage in healing rates with the addition of saphenous vein surgery to a four-layer compression treatment. We examined the role of saphenous vein surgery alone without postoperative compression (an essential methodological point if the true role of surgery is to be established) and have demonstrated significant haemodynamic improvement in these limbs following superficial venous surgery[1] and that the majority of ulcerated limbs with isolated superficial venous reflux will heal without the need for four-layer compression bandaging, community nurse time and associated drain on National Health Service resources. We agree that effective ulcer healing must be achieved and ulcer recurrence rates must also be reduced. To date, after 24 months of follow-up there have been no recurrent episodes of ulceration although this follow-up period is itself too short.

The identification of patients who may prove to have ulcerated limbs that are difficult to heal is laudable, but by doing so we cannot yet offer a more efficacious therapy and, as clinicians, we may have to accept that some patients with associated pathology may never achieve complete ulcer healing with compression or saphenous vein surgery.

To achieve and maintain ulcer healing in these patients the underlying pathology (ambulatory venous hypertension) must be reduced and the way forward in the management of venous ulceration is the accurate identification of patients with patterns of venous reflux that are effectively treatable by surgery and confining compression bandaging to those limbs that are not surgically treatable. The identification of such groups of patients can only be achieved by further laboratory studies.

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1 Scriven JM, Thrush AJ, Hartshorne T, London NJM. The haemodynamic effect of sapheno-femoral/popliteal disconnection in patients with venous ulceration. *Br J Surg* 1996; 83(Suppl 1): 50.

British Journal of Surgery 1997, 84, 1324–1325

Book reviews

Emergency Surgery and Critical Care. A Companion to Specialist Surgical Practice

S. Paterson-Brown (ed.). 252 × 193 mm. Pp. 321. Illustrated. 1997. London. W.B. Saunders. £40.

This multiauthor textbook is a compilation of 11 chapters on aspects of emergency surgery and critical care. Despite its all-embracing title, the scope of the book is generally confined to abdominal and gastrointestinal emergencies. It covers the management of the acute abdomen, surgical nutrition, non-variceal upper gastrointestinal bleeding, acute conditions of the small and large intestine, pancreaticobiliary system, and anorectum, sepsis, abdominal trauma and intensive care It is written both by surgeons in training and by senior and respected authorities in their subspecialties.

The preface states that the book is designed to meet the needs of those in higher surgical training and the busy practising surgeon. Much of the text is more suited for the student or junior trainee, while the heavily referenced and tabulated style elsewhere is more suited to the journal review article. The readability and impact of a textbook usually derives from simplicity and conciseness of text, combined with generosity with clear diagrams and well chosen photographic images. The closely typed layout and wordiness of this text in general militates against easy reading. The book would have benefited from firmer editing. It varies in quality and educational value from chapter to chapter. The chapter on surgical nutrition, for example, runs to 65 pages with 140 references. Conversely, Professor Spitz' chapter on paediatric emergencies stands out for its clarity of text and figures. The chapter sequence and structure also lends the air of a loose compilation. For example, there is no coherent treatment of emergencies of the lower oesophagus, stomach and duodenum.

One must question the value of a new text on emergency abdominal surgery. The preface states with pride that the book has been written in a very short time frame and will be updated frequently to ensure that current information is always available. Herein lies the rub; this is surely the role of reviews in specialty journals. An authoritative textbook should take a longer term view of a subject in years or decades, to distill knowledge from information, and substance from fashion and immediacy.

We all suffer from information overload in professional life, be it on the journal rack in the library or in the publishers' catalogues. Any effort on the part of our colleagues to simplify our lives must be welcomed. In an age wherein the commercial imperative obliges every publishing house to have a full catalogue of subspecialty texts, Mr Paterson-Brown and his coauthors are to be congratulated on a book that contains all the information necessary to cover the chosen subjects in depth. It will address very satisfactorily the needs of surgeons in training and those revising for higher examinations Whether the series of *Companions to Specialist Surgical Practice* will survive the test of time alongside some of the hallowed texts of emergency surgery the market alone will judge.

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Operative Laparoscopy and Thoracoscopy

B. V. MacFadyen Jr and J. L. Ponsky (eds). 287 × 220 mm. Pp. 959. Illustrated. 1996. Philadelphia, Pennsylvania: Lippincott-Raven. £180.25.

With 93 contributing authors and almost 1000 pages, this book risks areas of repetition and personal opinion. The editors have avoided this trap by having a reassuring continuity of style throughout the volume. Each chapter discusses the anatomy, preoperative planning, operating technique and complications for an enormous range of minimally invasive procedures. The illustrations and photographs are excellent, enabling an easy understanding of the steps in each procedure. 'Surgical pearls' in the margins offer concise tips on how to prevent or cope with certain problems associated with each procedure.

The first chapters that address the training, professional regulation and economics of laparoscopic surgery are interesting, but view these areas from an American perspective. The subsequent chapters concerning equipment, video-imaging technology, the use of diathermy and some basic surgical techniques are extremely well written, and useful for all new and practising laparoscopic surgeons. The only apparent gaps were thoracoscopic coronary artery surgery, gasless laparoscopy and a critical analysis of the place of laparoscopic surgery in malignant disease. Despite this, the book is as up to date as one could hope for in this constantly changing field. In short, it covers the subject thoroughly and would make an excellent reference work for the surgeon embarking on or assisting in advanced laparoscopic techniques. It covers operative details, patient selection and post-operative complications. It deserves a place on the bookshelf of all surgeons interested in minimally invasive techniques.

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Year Book of Surgery 1996

Roshan Lall Gupta. 228 × 151 mm. Pp. 362. Not illustrated. 1997. New Delhi: Jaypee Brothers Medical Publishers. Price not supplied.

This book is a collection of précised articles taken from leading British, American and Indian subcontinent publications covering the years 1995 to 1996. It contains over 200 abstracts relating to the subspecialties of general surgery and urology There is a good mix of both clinical and scientific papers. Many of the abstracts come with clinically relevant commentary from the editor. The stated target readership are surgeons in developing countries and, in particular, the Indian subcontinent. There can be no doubt that this book will prove useful to those individuals who have limited access to library resources. These potted accounts should also prove valuable to surgical trainees wishing to gain a general overview of the developing areas of surgery while preparing for examinations

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Outpatient Coloproctology Textbook and Color Atlas

G. Dodi and R. J. Spencer. 272 × 200 mm. Pp. 841. Illustrated. 1996. Padova: Piccin. Price not supplied.

This is a large, impressive-looking book containing 63 chapters. It is fairly freely illustrated with line diagrams and photographs, although some of these appear rather old fashioned. The first edition was in Italian in 1986, with an English edition published 10 years later It is written in American English and there are a number of textual errors which can be irritating to the reader

The volume is aimed at both the specialist coloproctologist and the family doctor, emphasizing outpatient and day-case coloproctology. Although it is fairly comprehensive in its approach, the emphasis on preferred treatments is not always in keeping with present British practice. Certain subjects, such as the surgical treatment of ulcerative colitis, are clearly neither up to date nor covered in much depth. Crohn's disease only merits 17 pages whereas the chapter on intestinal parasitosis is 23 pages in length. This cannot really be recommended to general practitioners as it is too weighty, or to surgeons in training as it fails to provide the right emphasis on present day best practice. General surgeons and coloproctologists may find it of interest but they have a wide choice of alternative texts which would be more useful.

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Cardiac Bioassist

A. Carpentier, J. C. Chachques and P. A. Grandjean (eds). 260 × 182 mm. Pp. 632. Illustrated. 1997. Armonk: Futura Publishing. US$125.

This timely update on the use of skeletal muscle for treating heart failure emerges 5 years after its predecessor, from the same editorial trio. However this edition is more comprehensive and the subjects covered are more broad based, reflecting a substantial increase in world interest in this form of biological assist. Although the title has changed, the book might as well have retained its original title of *Cardiomyoplasty* as this remains the subject of almost three-quarters of the volume. There are 50 chapters supported by an impressive list of contributors, many of whom have pioneered this field over the past 10 years. The text is divided into seven parts.

Part I describes the present clinical experience with dynamic cardiomyoplasty encompassing European, North and South American, and Russian experience. The overwhelming message is that a majority of patients undergoing this procedure for heart failure will be symptomatically improved Part II concentrates on non-invasive and invasive means of assessing native left ventricular function following cardiomyoplasty with the use of both load-dependent and load-independent measures, and helps to provide some insight into the likely mechanisms by which cardiomyoplasty patients are improved. Part III represents a major and important section of the book, focusing on skeletal muscle function following the cardiomyoplasty procedure. There has been concern in recent years about the integrity of the electrically stimulated muscle graft; various aspects of structure and function, particularly in relation to stimulation regimens and their effects on blood flow and bioenergetics of the muscle, are discussed. A miscellaneous collection appears in Part IV under the title 'Alternative Techniques'. These include graft options other than the latissimus dorsi muscle, the possibility of using two muscle grafts, or, alternatively, surrounding the aorta with the graft instead of the heart to generate more indirect ventricular support by diastolic counterpulsation Part V represents the only major divergence from the cardiomyoplasty theme concentrating on the alternative use of auxiliary pumping chambers derived from skeletal muscle. Part VI returns to the cardiomyoplasty concept but in the form of cellular or molecular modifications to compensate for loss of myocardial cells. This represents a new and exciting area in the skeletal muscle assist field. The final part of the book considers the current indications for, and future of, cardiomyoplasty in the form of a debate by two of the great pioneers in cardiac surgery. Dr Alain Carpentier and Dr Albert Starr.

In conclusion, I recommend this publication both for readers wishing to gain some insight into this fascinating area and also for those with an established interest in the field for whom the information will provide a fairly comprehensive update.

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Surgery for Gastrointestinal Cancer. A Multidisciplinary Approach

H. J. Wanebo (ed.). 285 × 218 mm. Pp. 864. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott-Raven. £124.25.

This book is written for gastrointestinal surgeons involved in cancer surgery. The first part gives an excellent overview of the present state of our understanding of gastrointestinal cancer; this is really one of the best parts of the book, offering good information on epidemiology, screening, and the genetics and biology of the primary tumour and metastases. The other part of the book focuses on the treatment of cancer from a multidisciplinary perspective. This, of course, is an excellent concept.

The volume is written by American authors, plus a few German authors and some Japanese This gives a rather 'extended surgery' flavour. In gastric cancer a systemic lymphadenectomy for stage IB, II, and IIIA is recommended. The DII lymph node resection is considered standard therapy. Support from randomized studies is not given (and not possible); the prospective randomized studies comparing total and subtotal gastrectomy (French trial) and extended *versus* non-extended surgery (Dutch trial) are not mentioned, although these studies indicate that there is no difference between the groups. For colorectal cancer, thorough regional lymphadenectomy is advocated and the Japanese experience is extensively described. Yet there is no randomized study to support this. The excellent results of the mesorectal excision of Heald are merely mentioned. Postoperative radiotherapy and chemotherapy is advocated as a standard adjuvant treatment but this is rather old fashioned and not a routine standard any more as the Swedish trial of preoperative radiotherapy has given other perspectives. I do miss a chapter on laparoscopic colon cancer resection, a topic that was not mentioned at all. Pancreatic cancer is extensively described, but again extended resection with regional lymphadenectomy is very much advocated, again without any proof. In the USA postoperative radiotherapy and 5-fluorouracil treatment is considered standard adjuvant treatment, which is not the case in European countries. The randomized EORTC study did not confirm the GITSG data. There is good information in this chapter on the treatment with radiotherapy and chemotherapy, especially in cases of locally advanced pancreatic cancer. American studies are mentioned to support this view; European studies that also support this are not.

It is a beautiful book with beautiful photographs and extensive bibliographies. Reading it is recommended for all gastrointestinal surgeons.

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Notices and announcements

12–17 October 1997
Management of Emergencies and Disasters: A Multidisciplinary Approach
Stoke, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

12–18 October 1997
Telemedicine and Telecare
Belfast, UK
Information Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

15–22 October 1997
Cancer in Children: Challenges and Controversies
London, UK
Information Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

23–24 October 1997
2nd Nottingham International Colorectal Cancer Symposium
Nottingham, UK
Information J. D Hardcastle, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

6–19 November 1997
Hong Kong International Cancer Conference and Asian Pacific Cancer Congress 1997
Hong Kong
Information Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

27–28 November 1997
31st Meeting of the Vascular Surgical Society of Great Britain and Ireland
London, UK
Information: T Szymanska, Vascular Surgical Society of Great Britain and Ireland, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information: M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information. O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information. Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

20–24 June 1998
Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer
Terme di Valdieri, Italy
Information. G Buccheri, Scientific Secretary, Ospedale A. Carle, 1-12100 Roccavione (CN), Italy

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For detailed guidance on the handling of statistical material, authors should consult *Br J Surg* 1991; 78: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of data, the *analysis* of data and the *interpretation* of results.

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Authors should beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

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Leading articles

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) combining endoscopy and high-frequency ultrasound has some distinct imaging advantages not provided by any other investigation, such as the precise delineation of the gastrointestinal wall structure, including the different wall layers. This enables locoregional staging of gastrointestinal cancer, diagnosis of submucosal lesions and the delineation of certain wall features in a variety of diseases, such as achalasia, portal hypertension, thickened gastric folds and inflammatory bowel disease (to name just a few). The high ultrasonic frequencies used (5–12 MHz) limit the penetration depth of the method, so that only structures and organs immediately adjacent to the gastrointestinal tract, such as the pancreas, the (distal) biliary tract and large vessels, can be imaged by EUS. In pancreatobiliary disease, diagnosis of small tumours, locoregional cancer staging and diagnosis of common bile duct stones are the main indications for EUS mentioned in the literature[1,2].

To clarify the clinical situation in which EUS is usually performed, it has to be recognized that the technique generally provides additional information (e.g. locoregional tumour stage) about a lesion that has been diagnosed primarily by other tests, such as endoscopy or radiology. The number of patients potentially suitable for EUS is limited. Nevertheless, imaging methods play an important role not only in establishing a primary diagnosis but also, once this is achieved, in providing relevant information that can be used directly to plan appropriate treatment. Simple as this may sound, the proper evaluation of an imaging method in achieving the latter goal is not at all easy. Since its fairly recent appearance on the gastroenterology imaging market, EUS has come into critical focus regarding its potential to influence 'outcome'. So-called 'outcome studies' are rarely worthy of the name and the difficulties in performing such studies on imaging methods using endosonography in tumour staging are outlined below. This, however, must be placed in the context of many seemingly established imaging tests which are widely used for particular indications (e.g. computed tomography for chronic abdominal pain) for which any positive influence on outcome is far from proven. Such tests have been around for many years and perhaps this alone justifies their application, at least until now.

The literature describes several hundreds of patients who have been examined by EUS for the staging of oesophageal (over 1000), gastric (over 2000), colorectal (over 2500) and pancreatic (over 500) cancer[1–3]. The accuracy rates in these studies, which are almost all surgically controlled, range from 75 to 85 per cent for T staging and from 65 to 80 per cent for N staging; the range of deviations between studies is rather small. EUS is, therefore, a fairly accurate technique for such an indication. Its limitations, resulting from inadequate examiner experience and, more importantly, inability to differentiate between inflammation and tumour, may be difficult to overcome. The latter limitation, however, applies to all imaging techniques. The reproducibility of EUS diagnosis between different examiners is limited.

Despite the vast majority of the above studies being prospective and surgically controlled, other factors needed to meet the standards of a proper evaluation may have been neglected. 'Blinding' is usually a problem in the clinical setting; this would require an external examiner just to perform or to evaluate a specific method under test. Doctors involved in the daily clinical routine, including radiology conferences, cannot with confidence be 'blinded to the results of other tests', even if this is stated in many of the published studies in the endoscopic and radiological literature. While performing an interobserver study on oesophagogastric cancer staging, my colleagues and I found that the accuracy rates for the blind videotape analysis were considerably lower than expected, even when the two examiners who published the results of prospective studies partly used the same cases[4–6]. Similar observations have been made by others, for instance in studies on magnification endoscopy and colorectal polyps[7,8]. It appears that much more information than the pure endosonographic image seems to be factored into the final diagnosis, such as the endoscopic tumour aspect[9] or even the clinical impression of the patient (dysphagia, weight loss, pain, etc.). In other words: you get the kind of information you expect to get. Given these limitations, which apply in general to all imaging methods, it is an important task for endoscopy and radiology societies to develop guidelines on how to perform proper accuracy studies on imaging methods.

Despite some scepticism, we can ascribe to EUS a good accuracy in locoregional tumour staging. Some limitations can probably be partially overcome in the future, e.g. with better image resolution, structure recognition systems and the application of EUS-guided fine-needle puncture for lymph nodes. This, however, does not mean that EUS necessarily changes outcome. In a recent study from the American Endosonography Club[10], EUS changed the management of patients in 74 per cent of cases, but this assessment was theoretical and based on the judgement of the examiners themselves. In my own institution a prospective study asked referring physicians exactly what it was that EUS had changed in their further management. The remaining diagnostic approach was significantly influenced in 52 per cent of cases, but treatment was changed by EUS in only 6 per cent[11]. This, however, may simply reflect the different approaches of the referring physicians; it does not mean that following a strictly standardized procedure for various diseases EUS might not influence further management.

Outcome is primarily influenced by therapy and an imaging method may, in the optimal case, improve selection of patients for an appropriate treatment. In this way it may have an indirect influence on outcome. Unfortunately, in gastrointestinal oncology the assumed superiority of some treatment concepts over others is rarely based on prospective randomized studies: if the direct influence of therapy on outcome is not established, how can one analyse easily the indirect influence of an imaging procedure? In EUS 'outcome' studies we often read that EUS prevented 'unnecessary' surgery. To start with, it is often difficult to tell when surgery is really unnecessary. But even if this was the case, any beneficial effects may result from the fact that less surgery is performed, be it due to EUS or other factors. A study supporting a superior role for EUS over other tests has to show that patients selected for a specific treatment on the basis of EUS do better than those selected for the same treatment on the basis of other tests. Since the expected differences are probably rather small, patient numbers must be huge to obtain statistically relevant differences. Furthermore, even if this superiority of EUS could be shown in a large multicentre trial, the results may not be applicable after any change in treatment concept.

The fact that EUS is a highly effective technique for gastrointestinal tumour staging is not doubted[12]; pancreatic imaging may be less secure since other methods (computed tomography, magnetic resonance imaging) have gained much ground in this field recently. Newer methods such as EUS-guided puncture or even EUS-guided treatment bring new perspectives and expanded indications. A critical look at the real clinical value of EUS would be welcome, but should simultaneously involve all other imaging tests used in gastroenterology. Furthermore, quality criteria should be developed for studies on imaging tests to which both endoscopists and radiologists should be required to adhere. Such criteria should also help the readers of journals to assess whether they are dealing with a real 'outcome' study or just another paper confirming the popularity of 'self-fulfilling prophecy' work.

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Towards international consensus in peripheral arterial thrombolysis

The advance of peripheral arterial thrombolysis from experimental treatment to routine therapy in the past decade has parallels with the rise of laparoscopic surgery: both became established in clinical practice before detailed evidence-based scientific evaluation was available. Clinicians are in no doubt that thrombolysis is a useful option in the management of acute leg ischaemia but it is only in the past few years that significant randomized trials have been reported on which guidelines for its use might be based[1–5]. The first consensus document on peripheral thrombolysis has recently been published in draft form by an international group of vascular surgeons, radiologists and angiologists[6], and awaits ratification by national vascular and radiological societies. The conclusions in the document are based on a detailed examination of the available scientific evidence, but in some areas the limitations of inadequate available data have been exposed.

There is considerable variation in reported results of peripheral thrombolysis. This is due to the different patient groups treated in different geographical areas, reflecting local referral patterns. In the UK, patients are nominally treated under the care of vascular surgeons. Most receive thrombolysis for acute limb-threatening ischaemia and are treated with low-dose intra-arterial infusion, usually of tissue plasminogen activator (tPA)[7]. In a few centres, accelerated techniques of lysis using boluses of tPA or pulsed spray methods are used in patients whose ischaemia is too severe to allow success with the slower low-dose infusion[8]. North American experience is more varied, reflecting the independent practice of surgeons and radiologists; patients with chronic critical ischaemia and claudication also receive thrombolysis. Accelerated thrombolysis with urokinase is preferred, including local manipulations such as thrombus infiltration and disruption[9]. Continental Europeans also favour urokinase. There, patients are often referred directly to angiologists whose practice is based on the treatment of claudication, and peripheral thrombolysis is used as an adjunct to angioplasty to open acute and more chronically occluded arteries with much lower complication rates than those reported from the UK[10]. Inferior results are obtained when thrombolysis is used for limb salvage, which explains why the UK experience is regarded elsewhere as disappointing.

The outcome of peripheral arterial thrombolysis depends on patient-related factors, the state of the limb and the type of arterial occlusion. Results from the Thrombolysis Or Peripheral Arterial Surgery (TOPAS) study[4] suggest that adverse patient-related factors include a history of stroke or heart failure, whereas the Surgery *versus* Thrombolysis for Ischemia of the Lower Extremity (STILE) study identified diabetes as a risk factor for reduced limb salvage[5]. The British Thrombolysis Study Group has a computerized database[7] which now includes over 600 episodes of intra-arterial thrombolytic treatment. The data reveal an exponential rise in both bleeding complications and mortality with increasing age over 70 years. The severity of ischaemia is important. Stable claudication (treated in continental Europe) appears to be associated with a very low complication rate compared with acute claudication, for which thrombolysis carries an appreciable morbidity rate and even mortality; the Thrombolysis Study Group database reveals a combined amputation and mortality rate of 10 per cent in this latter group. Limb salvage rates are poorer for acute critical ischaemia, especially when there is no audible Doppler ultrasonographic signal from an ankle artery or a neurosensory deficit is evident. Bypass graft occlusions are easier to lyse than native vessel occlusions[2]. Other occlusions that fare poorly are those that are long, embolic or not easily crossed with a guidewire.

Randomized trials have addressed some of the important questions. The Rochester study compared initial surgery against thrombolysis for acute limb-threatening ischaemia and found that lysis was the initial treatment of choice, largely because of the high perioperative mortality rate following surgery[3]. The original STILE study report concurred, noting an improved amputation-free survival rate in patients with acute ischaemia of less than 14 days' duration[2]. Many patients in the STILE study had chronic arterial occlusions and the latest analysis suggests that the main advantage of initial thrombolysis could be in those with graft occlusions[5]. Comparison of the efficacy of the different thrombolytic agents has been hampered by the lack of dose equivalence between the drugs; there is still no universal unit of lytic activity. No major trial has ever described superiority of urokinase or tPA[2], but streptokinase (which has previously been tested formally only in a small study[1]) has fallen from favour because of perceived disadvantages of antigenicity. There have been several randomized comparisons of thrombolytic techniques. Accelerated methods, such as pulse spray or bolus lysis, may reduce the duration of treatment, but they consume more lytic drug than low-dose infusions and have never proved to be superior overall[8,9].

In experienced hands, peripheral arterial thrombolysis is clearly a useful treatment, but it is apparent that the agent and technique are less important determinants of outcome than the medical condition of the patient and the leg. This has significant implications for those financing the development of new drugs and thrombolytic equipment. Further large-scale trials will, in future, be difficult, as prejudices gained as a result of previous studies become entrenched. The randomized trials to date have not used the same outcome definitions. The STILE study used a composite outcome including death, amputation, and recurrent or ongoing ischaemia[2,5], whereas the TOPAS study relied on amputation-free survival. Patient selection is the key and further refinements based on well conducted studies will be important. For example, evidence that initial thrombolysis affects survival, particularly in diabetics, will need to be revisited[3,5]. It is also time that the cost effectiveness of thrombolysis as an intervention and its risk:benefit ratios were examined in depth.

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Review

Hereditary breast cancer

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Background Hereditary breast cancer is thought to account for less than 10 per cent of all breast cancers. Recently there have been significant advances in understanding of the genetics, with the sequencing of the genes *BRCA1* and *BRCA2* which are associated with hereditary breast cancer.

Methods and results Current understanding of hereditary breast cancer and its impact on the management of women with this disease is reviewed.

Conclusion Problems in accurate testing for breast cancer-associated genes remain. No reliable simple test exists because of the large number of mutations present in these genes. The implications of different mutations remain poorly understood. Guidelines for the management of carriers of the breast cancer-associated genes remain controversial.

Breast cancer is the most commonly diagnosed fatal cancer in women in the European Union today[1]. The lifetime risk of a woman having breast cancer is estimated as one in 12. A family history of the disease in a first-degree relative significantly increases this risk. Hereditary breast cancer is characterized by early onset, a high incidence of bilateral disease, association with other malignancies and autosomal dominant inheritance[2]. Recently there have been significant advances in understanding of the genetics, with the sequencing of the genes *BRCA1* and *BRCA2* which are associated with hereditary breast cancer.

The terms familial breast cancer and hereditary breast cancer are frequently interchanged. A distinction is made between them in this review. The latter refers to cancer that occurs when the family history suggests a highly penetrant major gene for breast cancer, characterized by early age of onset, high incidence of bilateral disease and association with other tumours. This is distinct from familial breast cancer, which implies that two or more first-degree relatives have had breast cancer and some familial factors are thought to underlie development of the disease[3,4].

Hereditary breast cancer is believed to account for 5–9 per cent of all breast cancers[3,5,6] and inherited factors are thought to contribute to 25–35 per cent of cases diagnosed before the age of 30 years[6–8]. The relative risk of developing breast cancer in a first-degree relative of a woman with the disease increases from 3·1 in those who have early-onset disease, to 5·4 in those with bilateral disease, to 8·8 in those with bilateral early-onset breast cancer. Second-degree relatives have a similar risk of developing breast cancer to controls[9].

Breast cancer syndromes

Breast–ovarian cancer syndrome

The breast–ovarian cancer syndrome is characterized by an increased susceptibility to the development of breast and ovarian cancer due to a mutation in the *BRCA1* gene located on chromosome 17q12-21[7,10–12]. *BRCA1* mutations are also associated with an increased risk of prostate and colonic cancer[13,14].

BRCA1 is a large gene spanning approximately 100 kilobases of genomic DNA and consisting of 5592 base pairs of coding sequence contained in 22 exons[15]. There is one large exon, exon 11, which makes up about 60 per cent of the coding region[16]. The 22 exons code for a protein of 1863 amino acids. This protein contains a zinc-finger region close to the amino terminal which suggests that *BRCA1* may be involved in regulation of gene transcription[15]. At least 100 mutations of *BRCA1* have been reported to date[16]. Many different types of mutation are found including mis-sense and nonsense mutations, deletions, insertions and intronic mutations[15]. Seventy to eighty per cent of mutations of *BRCA1* are frameshift mutations causing premature protein termination[8].

Breast carcinomas in patients with hereditary breast cancer show loss of heterozygosity in the region of *BRCA1*. Loss of heterozygosity is a term that refers to the loss of an allele. This allele would normally function to suppress the development of a cancer. Loss of this allele, also known as a tumour suppressor gene, allows unchecked cell proliferation. Identifying loss of heterozygosity is an approach to identifying the location of the tumour suppressor gene. Loss of heterozygosity in the region of *BRCA1* in hereditary breast cancers suggests that *BRCA1* is a tumour suppressor gene[12].

Genetic alterations of *BRCA1* have been shown in approximately 10 per cent of sporadic ovarian cancers[17] but in no sporadic breast cancers[17–19]. In families with *BRCA1* mutations, inheritance follows an autosomal dominant pattern with each child of an affected parent at 50 per cent risk of inheriting the defective gene. The risk of inheriting a germline *BRCA1* mutation is similar whether the mutation is passed through the maternal or paternal germline. The true incidence of germline mutations in the general population remains unknown[8], but it is estimated that one in 200 to one in 400 women may be carriers of the *BRCA1* mutation[20,21]. This incidence is higher in Ashkenazi Jewish women, who have an incidence of one in 107 of a specific frameshift mutation at position 185 in exon 2 of *BRCA1*, which involves deletion of adenine and guanine – 185delAG[16].

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Table 1 The genes involved in breast cancer, the percentage of cases for which they are thought to be responsible and their penetrance

Gene	Percentage of all breast cancers	Percentage of hereditary breast cancer	Penetrance
BRCA1	1–4[13]	45[22]	87 per cent by age 80 years[23]
BRCA2	?	45[24]	87 per cent by age 80 years[25]
p53	< 1[26]	< 1[26]	89 per cent by age 50 years[27]
Cowden's disease	?	?	40 per cent by age 50 years[25]
Ataxia telangiectasia	?	?	11 per cent by age 50 years[26]
Gorlin's syndrome	?	?	?
Androgen receptor	?	?	?

BRCA1 mutations are thought to account for approximately 1–4 per cent of all cases of breast cancer (*Table 1*)[13,20]. Mutations of *BRCA1* are believed to account for at least 80 per cent of families with a history of multiple cases of early-onset breast and ovarian cancer[6,7,28]. Approximately 45 per cent of cases of early-onset breast cancer may be linked to *BRCA1*[3,6,7,28]. A recent study of 145 Canadian families with breast and ovarian cancer estimated that 76 per cent of these were linked to *BRCA1*. These families contained three or more cases of early-onset breast or ovarian cancer. All families contained at least one case of ovarian cancer[29]. Early onset in these patients referred to those developing breast cancer before the age of 60 years. The risk of developing breast cancer in *BRCA1* carriers is estimated to be 51–73 per cent by age 50 years and 82–87 per cent by age 70 years[3,8,13,23]. Lifetime risk of developing ovarian cancer is estimated to be 50–60 per cent[16,30]. Gayther *et al.*[31] have recently demonstrated that mutations in the 3′ third of the gene are associated with a lower proportion of ovarian cancer.

BRCA1 was previously thought not to be associated with an increased risk of male breast cancer. Recently, however, in a study of ten families with breast and ovarian cancer, a frameshift mutation of *BRCA1* was identified in a man with breast and prostate cancer[32]. Male carriers of *BRCA1* do appear to have an increased risk of prostate cancer, with an absolute risk estimated at 6–8 per cent by 70 years of age and a relative risk of 2·9–3·3, compared with non-carriers[13,14,23]. A recent study demonstrated loss of heterozygosity at 17q12-21 in 11 of 21 patients with prostate cancer, suggesting that *BRCA1* and other loci on chromosome 17q may be important in the pathogenesis of prostate cancer[3,33]. Both men and women with this *BRCA1* mutation also have an increased absolute risk of colonic cancer of about 6–8 per cent by 70 years of age, and a relative risk of colonic cancer of 3·3–4·1 compared with non-carriers[13–15,23].

Site-specific cancer syndrome

In 1994 a second gene, *BRCA2*, which predisposes individuals to breast cancer was mapped to chromosome 13q12-13[28,34]. *BRCA2* was located by performing a genomic linkage search using 15 families with multiple cases of early-onset breast cancer that were not linked to *BRCA1*[28]. Like *BRCA1*, *BRCA2* appears to be a tumour suppressor gene[18]. *BRCA2* codes for a protein of 2329 amino acids; the function of this protein remains unknown[34]. Twenty germline mutations likely to be due to *BRCA2* have been detected in breast cancer families to date; these mutations are mainly inactivating.

Mutations of *BRCA2* may be responsible for 45 per cent of cases of hereditary breast cancer. Families in which this abnormal gene is present show mainly a high incidence of breast cancer without ovarian cancer[14,28] and so the gene is thought to account for a high proportion of site-specific breast cancer. The presence of a *BRCA2* mutation is thought also to be a factor in the development of certain cases of male breast cancer[28,34] but, as the absolute risk of developing male breast cancer is still small, many families with *BRCA2* mutations will be characterized only by female breast cancer[28]. It is estimated that the risk of developing breast cancer in *BRCA2*-linked families is approximately 87 per cent by age 80 years, a value similar to that of *BRCA1* penetrance[28].

Li–Fraumeni syndrome

Mutation of the *p53* gene occurs in the Li–Fraumeni syndrome, a syndrome first described in 1969[35] and associated with early-onset and bilateral breast cancer and other tumours, such as soft tissue sarcomas, osteosarcomas, brain tumours, leukaemia and adrenocortical carcinoma. Other tumours that may occur in association are carcinoma of the lung or prostate or pancreas, and malignant melanoma[3,28]. Approximately 50 per cent of families with Li–Fraumeni syndrome do not have germline mutations of the *p53* gene[36,37]. Birch[36] suggests that a proportion of these families may have mutations of intronic or promoter regions. The risk of breast cancer is over 50 per cent by age 50 years in women with this syndrome[38]. Germline mutations of this gene are, however, probably responsible for less than 1 per cent of all breast cancers[38].

Ataxia telangiectasia

Ataxia telangiectasia is an autosomal recessive disorder in which both heterozygotes and homozygotes carrying the defective gene have an increased risk of cancer, especially breast cancer[6,39]. The defective gene has been mapped to a region on chromosome 11q22-23 and has recently been isolated[40]. The coding portion of the gene consists of 100 base pairs in which 40 mutations have been described[41]. It is estimated that the relative risk of breast cancer in a heterozygous female compared with that in controls is 5·1–6·8[6,9,42]. Exposure to radiation may increase the risk of breast cancer fivefold to sixfold in women who are heterozygous for the ataxia telangiectasia gene[39]. However, it is still to be determined whether mammography is associated with an increased risk of breast cancer in these women[39].

Androgen receptor gene

Mutations of the androgen receptor gene located on chromosome Xq11.2-q12 may be implicated in the development of breast cancer. Germline mutations of this gene may contribute to male breast cancer[6,43]. However, the majority of male breast cancers are not X linked and other genetic alterations must be considered in the pathogenesis.

Other genes

Loss of heterozygosity has been demonstrated in breast cancers from individuals with a strong family history of breast cancer in genetic loci other than those mentioned above. These loci include loss of heterozygosity at 8p, 16q and 19p in approximately 20 per cent of cases[44]. Such findings suggest that there may be other tumour suppressor genes involved in the pathogenesis of hereditary breast cancer which have yet to be identified. Cowden's disease is characterized by early onset of cancer, a high incidence of bilateral disease and hamartomas of the skin and gastrointestinal tract[9]. The genetic mutation involved in the pathogenesis of Cowden's disease has recently been mapped to chromosome 10[45]. Gorlin's syndrome, which manifests as multiple basal cell carcinomas of the skin, cysts of the jaw bones and erythematous pitting of the palms and soles, is also associated with a predisposition to the development of breast cancer. The gene for Gorlin's syndrome has recently been cloned[46].

Problems in identifying patients at risk of hereditary breast cancer

Identification of women at high risk of hereditary breast cancer begins by taking an accurate family history[3]. At particular risk are women with a family history of early-onset breast cancer, a family history of bilateral breast cancer, those with several affected family members and a family history of other malignancies at an early age. However, a family history of breast cancer may not be a reliable indicator of those who are likely to carry a germline mutation of a breast cancer susceptibility gene. Approximately 6–19 per cent of individuals with breast cancer have an affected relative, but this does not reliably identify women who are likely to be carriers of germline alterations[8]. In large families a positive family history may reflect the high incidence of sporadic disease, and in small families the absence of family history does not rule out the presence of a genetic mutation[8]. *BRCA1* mutations may also be transmitted through male relatives in a family with no male or female breast cancers being manifest[47]. Other individuals may exhibit *de novo* germline mutations and consequently have no family history of breast cancer[47]. Identification of *BRCA1* carriers by family history may also be obscured by incomplete penetrance of this gene. Lifetime disease penetrance of *BRCA1* is believed to be 88 per cent[48]. Carriers of *BRCA1* may not be identified in the remaining cases as they will not develop disease, thereby obscuring the pattern of inheritance.

Genetic testing for breast cancer: current issues

Genetic tests are now available that can identify mutations of *BRCA1* and *p53* genes. There are approximately 12 laboratories carrying out *BRCA1* genetic testing within the guidelines of a protocol in the United States[24]. At present, genetic testing for *BRCA1* is indicated in an affected person with a family history of early onset of disease, or bilateral disease, or a strong family history of breast and ovarian cancer. Before referral for screening, some centres request that three first-degree relatives be affected; others request four. It is important that the DNA of at least two affected relatives is available to confirm that the mutation found is a stable abnormality.

Routine genetic testing involving sequencing of the complete *BRCA1* gene would not be practical owing to the large size of the gene. Fortunately, there are three specific mutations that appear to be relatively common[49], and these may make a simple diagnostic test for *BRCA1* mutations possible. They are the 5382insC mutation in codon 1756, the 185delAG mutation in codon 23 and the 4184del4 mutation in codon 1355[49]. Mutation detection after identification of an affected individual is not usually primarily by sequencing. In the absence of the three common mutations, screening for unknown mutations is carried out, using techniques such as the protein truncation test, single-stranded conformational polymorphisms or chemical cleavage. Only patients in whom abnormalities are shown by these techniques have their *BRCA1* gene sequenced.

At present, the risk associated with different germline mutations is not known. However, the relative risk of breast *versus* ovarian cancer varies with the site of the *BRCA1* mutation. There have also been difficulties in differentiating between changes of genetic sequence that do not affect the function of the gene, i.e. between non-pathogenic polymorphisms and those that are true mutations associated with a susceptibility to breast cancer[24]. Only clearly pathogenic gene mutations can be used in a clinical setting for predictive purposes. False negatives may occur as not every mutation will be detected[16], and at present a negative test for *BRCA1* mutation is useful only if a *BRCA1* mutation has been identified in a first-degree relative[49].

Carriers of *p53* mutations may be identified by detection of mutations in the *p53* gene if a strong clinical suspicion of Li–Fraumeni syndrome exists. However, only 50 per cent of individuals with this syndrome have a mutation of the *p53* gene. The penetrance and phenotypic expression of genetic mutations in Li–Fraumeni syndrome remain unknown, as does the influence of external factors on the development of malignancy in carriers[36].

There are a number of social, psychological and ethical problems associated with genetic testing. There may be adverse psychological effects to being identified as a carrier. It may be difficult for women who test positive to obtain life and health insurance. There may be employment discrimination, and issues such as who will finance prophylactic treatment (prophylactic bilateral mastectomy or prophylactic oöphorectomy) may need to be faced[3,50].

Women who are at increased risk of breast cancer should preferentially attend a 'high-risk' clinic where facilities for accurate risk estimation, genetic counselling and testing exist. However, there are no data at present on the outcome for women seen in such clinics.

Management of gene carriers

The management of known carriers of breast cancer susceptibility genes remains controversial. Options include prophylaxis against the development of breast cancer, by either mastectomy or tamoxifen, or careful follow-up with screening for overt disease.

Prophylactic measures in hereditary breast cancer

At present, for most women the only option available clinically for prophylaxis of breast cancer is bilateral mastectomy[51]. Both subcutaneous and total mastectomy have been used for prophylaxis[51]. Subcutaneous mastectomy, although associated with a better cosmetic outcome than total mastectomy, leaves residual breast tissue behind the nipple and so does not provide complete protection against the future development of cancer[52,53]. The remaining breast tissue, although small in amount, remains at risk of malignant transformation. The literature includes reports of breast cancer occurring after both subcutaneous and total mastectomy[54,55]. The psychological morbidity associated with prophylactic mastectomy is similar to that following mastectomy for the treatment of established cancer[56].

Tamoxifen is currently being evaluated in randomized trials in the USA, UK and Italy to determine its value in prophylaxis in a high-risk population[51,57,58]. It is estimated that tamoxifen may reduce the incidence of breast cancer in high-risk women by 30 per cent[59]. About 16 000 women over 35 years of age at increased risk of cancer have been randomized to receive oral tamoxifen (20 mg per day) or placebo for 5 years[59]. This trial has been based on findings that demonstrated a reduction in new primary breast cancers in patients who took adjuvant tamoxifen therapy. Clinical trials have demonstrated a reduction in the incidence of contralateral cancer of 39 per cent in women receiving adjuvant tamoxifen therapy[51].

Tamoxifen is not, however, without risk, including an increased incidence of endometrial and liver cancer. Fornander *et al.*[60] found the relative risk of developing endometrial cancer in women taking tamoxifen is increased by up to 6·4 compared with controls. Other side-effects of tamoxifen therapy include hot flushes, nausea, vomiting, fluid retention, weight gain, thrombocytopenia and an increased incidence of thrombotic complications[61].

Benefits of tamoxifen in treatment for breast cancer have been widely accepted as outweighing the risks. However, in the case of tamoxifen therapy for prevention of breast cancer in healthy women, benefit is not clear and the results of trials are awaited[62] Clinical trials are also taking place to investigate the benefit of either fenretinide, a synthetic retinoid (4-hydroxyphenylretinamide), or a low-fat diet in the prevention of breast cancer in premenopausal women[51,63].

Screening those at risk of hereditary breast cancer

Standard recommendations for screening for hereditary breast cancer are annual clinical examination and mammography from 35 years of age, or from 5 years before the age at which the youngest affected family member developed the disease[37]. Despite the absence of data to show that the mortality rate from breast cancer is reduced by screening mammography in *BRCA1* or *BRCA2* mutation carriers, Lynch *et al.*[3] recommended that mammography should be carried out biennially from the age of 25–35 years and annually thereafter. Mammography is the method used in mass screening for breast cancer[64]. Problems associated with its use in screening for hereditary breast cancer include the higher density of the breasts of younger women requiring screening, with a reduced ability to detect clinically important breast cancers[65]. However, in a retrospective study of the mammograms of women aged under 35 years diagnosed with breast cancer, 90 per cent of lesions were visible[66]. These results suggest that mammography may be useful for detecting breast cancer in young women at high risk. However, frequent exposure of the breasts to low radiation doses from a young age may carry the associated problem of breast cancer induction. As yet, the risk of radiation-induced cancer in *BRCA1* mutation carriers is unknown, but it may be particularly important in women who are heterozygous for the ataxia telangiectasia gene for whom the risk of radiation-induced cancer may outweigh the benefits[3,39]. The best way of screening the genetically high-risk patient has yet to be determined.

The future

A great deal of uncertainty remains about *BRCA* mutations. Which mutations have a higher penetrance? What distinguishes those who develop cancer from those who do not? Does some other risk factor, whether genetic, environmental or lifestyle, play a part? Such questions are addressed in a project entitled the Cooperative Breast Cancer Registry, organized by the National Cancer Institute in the United States. Over the next 4 years, six participating academic centres in the USA will collect blood cells and tumour specimens from about 6000 women with breast cancer and 20 000 of their relatives. Many women will be chosen based on their degree of familial risk, whereas others will be unselected for family history. The centres will also collect clinical and epidemiological data on age of menarche, contraceptive use, pregnancies, home therapies, smoking history, environmental exposures, exercise habits and diet. Records will be updated every year with data on who has developed cancer, and the progression and treatment of the disease.

In Europe, the European Breast Cancer Consortium is coordinating prospective studies of known *BRCA1* and *BRCA2* carriers. By following these patients over the coming years, several issues may be addressed. One is risk, not only of breast and ovarian cancer, but also of other types of neoplasm that are somewhat more frequent in carriers. Another is whether mutations in different regions of each gene cause different spectra of cancers. The results of such studies should help women with *BRCA1* or *BRCA2* mutations make informed decisions about how to protect themselves from breast and ovarian tumours. At present these women face difficult decisions with inadequate information.

The genetics of breast cancer is a field that has evolved rapidly since the discovery of *BRCA1* in 1994[7]. It is tempting to speculate on the clinical usefulness of genetic testing Some authors predict that *BRCA1* will be used as a screening tool on a widespread basis in the future[51]. However, the current position of the National Advisory Council for Human Genome Research in the United States is that genetic testing for breast cancer is not advisable until further experience has been gained and the impact of genetic screening has been studied in greater detail.

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Review

Bacterial translocation in multiple organ failure: cause or epiphenomenon still unproven

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Background A body of evidence exists for the occurrence of bacterial translocation and its relationship to multiple organ failure (MOF).

Methods Relevant articles on bacterial translocation (the phenomenon defined as the passage of microbes and endotoxin across the intestinal barrier) in patients prone to develop MOF and in representative animal studies were selected. To interpret and evaluate the evidence for bacterial translocation in current literature, the endpoints generally used are discussed.

Results Fractional data from individual manuscripts were tabulated and assessed for statistical significance with χ^2 analysis. Various clinically relevant stimuli, postulated as important causative factors for the development of MOF, appeared to be interrelated and related to bacterial translocation itself.

Conclusions Convincing evidence exists that bacterial translocation can occur in humans during various disease processes. However, it remains to be determined whether a causal relationship between bacterial translocation and MOF exists. MOF is probably multifactorial and not uniform in origin; when evaluating translocation as a causative factor in the absence of an infective focus, the type of initiating event and the period of time after which MOF develops should be taken into account. The origin of early MOF is probably a non-bacterial, extensive, inflammatory response resulting in massive generalized endothelial cell activation. Late MOF may be caused primarily by bacterial translocation inducing an imbalance between proinflammatory and anti-inflammatory cytokines.

Multiple organ failure (MOF) is an important cause of morbidity and mortality in hospitals. The mortality rate ranges from 20 to 80 per cent, depending on the definition of MOF and the number of organs that fail[1–5]. In general, MOF is characterized by progressive dysfunction of vital organs and organ systems. Many clinical definitions and scoring systems have been proposed, although none has been designed to identify specific patient risk or allow clinical decision-making for an individual patient[6].

Much research has been performed to elucidate the pathogenesis of MOF in order to find a rationale for new therapeutic options. Initially, an infective model of MOF was proposed and it was concluded that MOF was caused by an untreated or inadequately treated focus of infection[4,7]. However, in the mid-1980s it became clear that not all patients with MOF had untreated infections. In fact, Goris *et al.*[1] showed, in a retrospective study of 55 trauma patients with MOF, that only 33 per cent had a definite bacterial focus with one or more positive blood cultures. Others diagnosed sepsis, defined as a focus of infection with bacteraemia, in only 19 of 34 patients with MOF after trauma[8]. Therefore, an alternative inflammatory model was proposed, in which the fundamental pathophysiological event in MOF was self-induced tissue damage mediated by the release of endogenous inflammatory mediators (i.e. cytokines)[9,10]. This was supported by studies demonstrating that infusion of cytokines produces physiological changes comparable to those in critically ill patients[11–13], and by the finding that the concentration of cytokines was significantly higher in patients with MOF than in those without[9,14].

In the early 1990s, MOF was interpreted as the most severe derangement of a systemic inflammatory response syndrome (SIRS)[15] that develops as a result of a variety of severe clinical insults[16,17]. It has been hypothesized that it either develops early after a massive insult which consequently results in a severe systemic inflammatory response or develops gradually via a continuum of physiological and metabolic changes caused by an ongoing systemic inflammatory response[10,16–19]. Recently, the above theory on the pathogenesis of MOF has been refined. Bone[18,19] has argued that the original insult results initially in the synthesis of proinflammatory mediators (tumour necrosis factor (TNF) and interleukin (IL) 1) and, if a critical level of proinflammatory mediators is reached locally, that systemic spillover may occur[20]. A systemic compensatory anti-inflammatory response is thereby induced to downregulate the proinflammatory reaction and restore homeostasis. In some patients excessive amounts of proinflammatory mediators are released which overwhelm

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the compensatory anti-inflammatory response, leading to a sustained proinflammatory response and organ failure. It has further been hypothesized that in some patients the compensatory anti-inflammatory reaction may be excessive, resulting in immunosuppression. This immunosuppression has been termed 'immunoparalysis' by Volk and co-workers[21] or 'the compensatory anti-inflammatory response syndrome' by Bone[19]. Although such a mechanism for the pathogenesis of MOF remains hypothetical, the results of several studies substantiate the theory[22–26]. To understand the mechanisms that underlie MOF, one must first understand how the initial SIRS develops.

SIRS is defined by two or more of the following conditions: (a) temperature greater than 38°C or less than 36°C; (b) heart rate greater than 90 beats per min; (c) respiratory rate greater than 20 breaths per min or an arterial partial pressure of carbon dioxide lower than 4·3 kPa; and (d) white blood cell count greater than 12 000 or less than 4000 cells per mm^3 or with more than 10 per cent immature forms. When SIRS is the result of a confirmed infective focus, it is termed sepsis. It has been postulated that SIRS is ultimately characterized by generalized activation of the endothelium[27–30]. Activation of endothelial cells is induced by numerous agents, such as oxidants, endotoxin, TNF and IL-1, and results in adherence of circulating leucocytes to the endothelium and transmigration of these cells (*Fig. 1*). Adherent neutrophils are primed to produce oxidants, proteases and cytokines, which ultimately result in tissue injury[31]. Oxidants are generated during ischaemia–reperfusion injury. Recently it has become known that they are initially derived from oxygen by a process mediated by xanthine oxidase on the endothelial cell surface and thereafter are generated by primed neutrophils[31]. Due to ischaemia, cellular energy stores are depleted, resulting in a reduced capacity to regenerate adenosine 5′-triphosphate. Instead, hypoxanthine is produced and, in addition, xanthine dehydrogenase is converted to xanthine oxidase. On reperfusion, oxidants are formed by the enzymatic action of xanthine oxidase, which converts hypoxanthine via production of xanthine to urate. The oxidants can induce tissue injury directly and, via the activation of endothelial cells, subsequently result in the production of neutrophil-derived tissue-damaging oxidants, proteases and cytokines. The cytokine production attracts mononuclear cells, which are capable of additional cytokine production and neutrophil activation. This can lead to spillover of the locally produced cytokines and primed neutrophils into the systemic circulation[20] and to remote tissue injury, due to the release of excessive amounts of proinflammatory cytokines, or to an overwhelming compensatory anti-inflammatory reaction, or to an imbalance between proinflammatory and anti-inflammatory cytokines[18,19].

The activation of the endothelium can be initiated under many clinical circumstances (e.g. shock, trauma, thermal injury and bacteraemia); under these circumstances activating agents are present. Generalized low-flow states (e.g. cardiogenic and haemorrhagic shock) and events often accompanied by hypovolaemia (e.g. trauma and thermal injury) can directly cause ischaemia–reperfusion injury of multiple organs[1,7,29,31,32] as a result of hypoperfusion induced by hypovolaemia and subsequent reperfusion of organs after resuscitation. In addition, substantial evidence derived from animal experiments has revealed that an ischaemia–reperfusion insult to one organ can indirectly injure remote organs, especially the lung[33–39]. During bacteraemia, such as that caused by an infective focus, various bacterial toxins are produced. Many Gram-negative organisms produce endotoxins which are lipopolysaccharide components of the outer cell membrane[40]. Among many other effects, endotoxins induce the production of cytokines by mononuclear cells

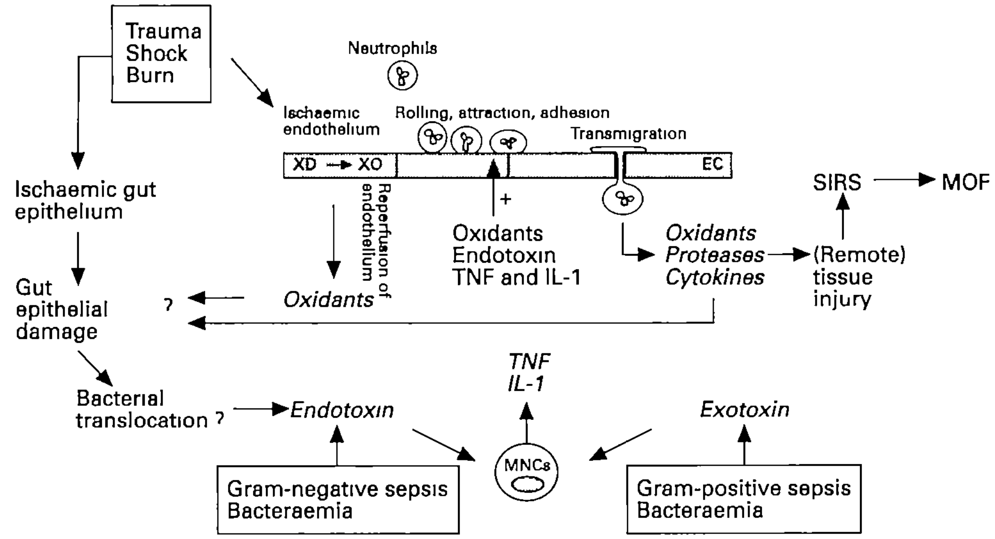

Fig. 1 Bacterial translocation in relation to the pathophysiology of multiple organ failure (MOF). Different clinical events mediate the release of agents (endotoxin, oxidants, cytokines) that stimulate the endothelium. Moreover, circulating neutrophils are attracted to the endothelium. The neutrophils transmigrate and release oxidants and proteases, subsequently causing (massive) tissue injury leading to systemic inflammatory response syndrome (SIRS) and MOF. Trauma, shock and burn injury may immediately cause massive inflammation of the endothelium, SIRS and MOF, or via bacterial translocation lead to an ongoing inflammatory state resulting in MOF. EC, endothelial cell; IL-1, interleukin 1; MNCs, mononuclear cells (monocytes, macrophages), TNF, tumour necrosis factor; XD, xanthine dehydrogenase; XO, xanthine oxidase; + indicates activation of the process of adhesion and transmigration of neutrophils

and endothelium, and activate the complement and coagulation systems. Gram-positive bacteria, particularly staphylococci and streptococci, produce exotoxins that stimulate, among other cytokines, TNF and IL-1 production by acting as superantigens[41,42].

In patients lacking a definite focus of infection, migration of residential micro-organisms and endotoxin across the intestinal mucosa, a process called bacterial translocation[43], has been postulated as an important causative factor for the development of MOF. In this scenario, intestinally derived bacteria and endotoxin might induce the production of cytokines and the activation of the endothelium, analogous to bacteria derived from an infective focus. Through this process, the gut may consequently comprise a reservoir of triggering compounds that initiate, perpetuate or intensify the systemic inflammatory response, ultimately leading to MOF. However, the significance of this proposed scenario is a matter of ongoing dispute. In this review the phenomenon of bacterial translocation is described and then the methods and endpoints used in current literature when trying to discern a connection between bacterial translocation and MOF are discussed. This is done to interpret and evaluate the evidence for bacterial translocation and its relationship to MOF, and to suggest some tools for future study design.

Bacterial translocation

Bacterial translocation was first described a century ago in animal experiments[44–46]. These findings were confirmed early after the Second World War by Fine and coworkers[47–49], who were able to detect viable bacteria in the peritoneal cavity after chemical irritation of the peritoneum of dogs. Schatten *et al.*[50] showed that bacteria could migrate from the gastrointestinal tract into the portal circulation in the absence of an infective process in humans. By collecting lymph from the cisterna chyli, bacterial transport beyond the peritoneal cavity into the intestinal lymphatics of the rat was demonstrated[51]. Subsequently it became clear that, in addition to Gram-negative bacteria, endotoxin[52–54], Gram-positive bacteria[54] and fungi[55] could also pass through the mucosal barrier.

Berg and Garlington[43], in 1979, coined the phrase bacterial translocation, which was defined as the passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa into the lamina propria and then to the mesenteric lymph nodes and, possibly, to distant organs. This definition was later extended to include the passage of all microbes and their toxic products across the intestinal barrier.

Factors influencing the incidence of bacterial translocation

Mechanisms controlling bacterial translocation depend on factors relating to the microbe itself and on host factors[56]. Facultative intracellular pathogens (*Salmonella* species, *Listeria monocytogenes*) translocate relatively easily. Anaerobic bacteria seldom translocate[57,58]; on the contrary, they play a key role in preventing enteric colonization by potentially pathogenic (facultatively aerobic Gram-negative) bacteria[59]. This situation has been recognized in clinical practice in the treatment of patients with antimicrobial agents that selectively eradicate the facultatively aerobic Gram-negative bacteria while retaining the anaerobic flora (selective digestive decontamination (SDD)).

The host defence directed against invasion of microbes from the gut comprises numerous factors, such as gastric acid, pancreatic enzymes, bile, mucus, the epithelial cell barrier with its intercellular junctions, bowel motility, and an antigen-specific local immune system, termed the gut-associated lymphoid tissue (GALT)[60,61]. Various host cells, such as macrophages[62], enterocytes[54,63] and T lymphocytes[64,65], have been proposed as playing a role in controlling bacterial translocation. However, the precise role of each cell in the different steps of translocation (invasion of the epithelium, transport to the mesenteric lymph nodes, etc.) has not been established yet.

Bacterial translocation has been described under various circumstances in which the above defence mechanisms have been impaired. Most evidence has been derived from rodent models, although human studies have also been performed. *Table 1* summarizes representative studies designed to monitor bacterial translocation in animals. *Tables 2* and *3* summarize studies on translocation with emphasis on situations relevant to patients prove to develop MOF. To interpret and evaluate evidence for translocation in the current literature, the endpoints generally used must be considered.

Animal studies and their endpoints

A considerable number of animal experiments have been carried out to investigate whether experimental models of shock, trauma and thermal injury are accompanied by bacterial translocation; most revealed translocation to the mesenteric lymph nodes (*Table 1*). The endpoints most commonly used to prove translocation in animal models consist of culture of bacteria from mesenteric lymph nodes, portal or peripheral blood, or the detection of endotoxin in portal or peripheral blood. However, as has been noted previously, the presence of bacteria in mesenteric lymph nodes may reflect a normal physiological function of the GALT that is necessary for the generation of immunocompetent cells[56]. In the various animal models, bacteria are rarely cultured from peripheral blood. An explanation for this may be that both the lungs and the liver provide a host defence mechanism in eliminating micro-organisms by tissue macrophages, from the central venous and portal blood respectively[103–105]. It is hypothesized, but not yet proven conclusively, that elimination of micro-organisms by liver tissue macrophages may be something of a double-edged sword, because these cells may also be activated by micro-organisms and respond by producing cytokines[106]. Such a response may modulate or amplify an inflammatory process and so directly or indirectly contribute to MOF.

Mucosal injury and mucosal atrophy have also been used as endpoints, particularly in animal studies, to support the translocation hypothesis. However, it must be recognized that most animal studies investigating a possible relationship between gut atrophy, mucosal injury, increased permeability and translocation either focus exclusively on changes in the small bowel or detect only small bowel abnormalities[78,83,107–114]. Only a few studies have analysed and demonstrated changes in the colonic mucosa[33,34], in spite of the fact that it is this intestinal segment that contains the vast majority of intestinal microbes under normal conditions. Animal studies should be performed in which the role of the liver is evaluated, for example by carrying out measurements in the portal

Table 1 Representative studies designed to monitor bacterial translocation in animals

Reference	Animal	Treatment	Effect of treatment	Translocation assay	Translocation increased
Runkel *et al*[66]	Rat	Morphine	Decreased bowel motility	Culture of MLNs and distant organs	Yes
Kueppers *et al*[67]	Rat	Morphine and TPN	Decreased bowel motility, CGEB	Culture of MLNs and distant organs	Yes
Maxson *et al.*[68]	Rat	Clonidine	Mucus depletion	*Escherichia coli* transport across ileum mounted in Ussing chamber	Yes
Barber *et al*[69]	Rat	Oral liquid diet	CGEB	Culture of MLNs and distant organs	Yes
Illig *et al.*[70]	Rat	TPN or oral TPN	CGEB	Culture of MLNs	No
Haskel *et al.*[71]	Mouse	Oral TPN	CGEB	Culture of MLNs	Yes
Speath *et al.*[72]	Rat	TPN	CGEB	Culture of MLNs	Yes
	Rat	Oral TPN	CGEB	Culture of MLNs	Yes
Shou *et al.*[73]	Rat	TPN	CGEB	Culture of MLNs	Yes
Deitch *et al*[74]	Rat	TPN or oral TPN	CGEB	Culture of MLNs	Yes
				E. coli transport across ileum mounted in Ussing chamber	Yes
Deitch *et al.*[75], Baker *et al.*[76]	Rat	Shock*	CGEB	Culture of MLNs, liver, spleen	Yes
Deitch *et al.*[77]	Rat	Shock*	CGEB	Culture of MLNs	Yes
		Shock* and SDD	CGEB	Culture of MLNs	No
Yong-Ming *et al.*[78]	Rat	Shock*	CGEB	Plasma endotoxin levels	Yes
				Histological visualization of bacteria in intestinal mucosa	Yes
Tokyay *et al*[79,80]	Minipig	40 per cent TBSA burn	Splanchnic vasoconstriction	Endotoxin levels in superior mesenteric vein	Yes
				Culture of MLNs	Yes
Fukushima *et al*[81]	Mouse	20 per cent TBSA burn	CGEB	Oral radiolabelled *E coli*; label detected in MLNs, distant organs	Yes
Zapata-Sirvent *et al.*[82]	Mouse	32 per cent TBSA burn	CGEB	Culture of MLNs	Yes
		Burn and oral liquid diet	CGEB	Culture of MLNs	Yes†
Go *et al.*[83]	Rat	Intraperitoneal lipopolysaccharide	CGEB	Culture of MLNs	Yes
				E coli transport across ileum mounted in Ussing chamber	Yes
Zhi-Yong *et al*[84]	Dog	Splanchnic ischaemia	CGEB	Blood culture	Yes
				Histological visualization of bacteria in intestinal mucosa	Yes

MLN, mesenteric lymph node, TPN, total parenteral nutrition (oral TPN indicates the TPN liquid was fed orally rather than parenterally); oral liquid diet indicates that animals were fed orally with various liquid defined-formula diets; CGEB, compromised gut epithelial barrier; SDD, selective digestive decontamination; TBSA, total body surface area. *Haemorrhagic shock followed by reperfusion; †translocation increased significantly compared with that in normal mice and burned mice fed rodent chow

and hepatic venous blood, and in which intestinal permeability changes are studied in the colon.

Human studies

Bacterial translocation has been shown to occur in various patient populations, ranging from the mildly to the critically ill (*Tables 2* and *3*). It occurs in patients operated on electively[87], in organ donors[98], in patients with intestinal obstruction[86,87,95], colorectal cancer[96,97], obstructive jaundice[115], ischaemia–reperfusion injury of the gut during cardiopulmonary bypass surgery[102], haemorrhagic shock[89,92,100], acute pancreatitis[94] and granulocytopenia[116]. After trauma[90,91,93,99], however, translocation has rarely been demonstrated by assessment of endotoxin concentration in portal[91] and systemic[91,99] blood, or by bacterial culture of portal[91] and systemic[91,99] blood.

Various interventions aimed at eliminating the putative causative pathogens have been tested for efficacy in patients at risk for MOF. Some have targeted circulating endotoxin in the blood; others have focused on selective intraluminal eradication of facultatively aerobic Gram-negative bacteria The impact of SDD on reducing the respiratory tract infection rate has been firmly established. SDD of the gut before oesophageal resection[117] or immediately after diagnosing severe acute pancreatitis[94] reduces the infection rate in the respiratory tract[117] and the general incidence of infectious complications following pancreatitis[94]. In critically ill patients, SDD also reduces the infection rate, especially in the respiratory tract[118–122]. This is probably due to SDD preventing aspiration of contaminated upper gastrointestinal tract secretions. The upper gastrointestinal tract may be colonized by indigenous bacterial flora as a result of the duodenal reflux and decreased bowel motility that are often found in patients in the intensive care unit[123].

Unfortunately, the reduced infection rate in these studies did not result in a reduction of the incidence of MOF[120] or mortality[117,119–121]. In one study on SDD in acute sterile necrotizing pancreatitis[94] 11 patients (22 per cent) in the SDD group died, as compared with 18 (35 per cent) in the control group ($P = 0{\cdot}19$). Six patients in each group died from MOF with documented sterile pancreatic necrosis. Moreover, there was no significant difference between the groups in the numbers of patients who died

Table 2 Representative studies designed to monitor bacterial translocation in humans, with translocation assayed as the recovery of viable bacteria from extraintestinal sites

	Clinical condition			No. of patients with a positive result		
Reference	Test patients	Controls	Tissue cultured for bacteria	Test patients	Controls	*P**
Ambrose *et al.*[85]	Crohn's disease	Elective laparotomy	MLNs	15 of 46	2 of 43	<0·01
			Serosa	12 of 46	6 of 43	n.s.
Deitch[86]	Bowel obstruction	Other abdominal surgery	MLNs	10 of 17	1 of 25	<0·01
Sedman *et al.*[87]	Laparotomy	None	MLNs	21 of 242	—	—
			Peripheral blood	2 of 242	—	—
			Serosa	7 of 242	—	—
Sagar *et al.*[88]	Bowel obstruction	Other abdominal surgery	MLNs	14 of 36	16 of 218	<0·01
Rush *et al.*[89]	Trauma (BP<80 mmHg)	Trauma (BP>80 mmHg)	Peripheral blood	10 of 18	3 of 32	<0·01
Peitzman *et al.*[90]	Trauma	Intestinal disease	MLNs	0 of 25	3 of 4	<0·01
Moore *et al.*[91]	Trauma	None	MLNs	4 of 12	—	—
	Trauma (BP<90 mmHg)	Trauma (BP>90 mmHg)	Peripheral blood	3 of 11	0 of 20	0·07
Brathwaite *et al*[92]	Trauma with shock	Trauma without shock	MLNs	1 of 15	0 of 5	n.s.
Reed *et al.*[93]	Trauma	None	MLNs	4 of 16	—	—
Luiten *et al.*[94]	Acute pancreatitis (no SDD)	Acute pancreatitis (with SDD)	Pancreas	17 of 52	4 of 50	<0·01
Laffineur *et al.*[95]	Crohn's disease	None	MLNs	7 of 28	—	—
Vincent *et al.*[96]	Colorectal cancer	Other digestive diseases	MLNs	13 of 20	6 of 20	0·06
Koha *et al.*[97]	Colorectal cancer	None	MLNs	14 of 22	—	—
van Goor *et al.*[98]	Critically ill organ donors	None	MLNs	11 of 21	—	—

MLN, mesenteric lymph node; BP, blood pressure; n.s., not significant; SDD, selective digestive decontamination. *Fractional data from individual manuscripts were analysed by the present authors with the χ^2 test with continuity correction by means of StatView SE + Graphics (Abacus Concepts, Berkeley, California, USA)

Table 3 Representative studies designed to monitor bacterial translocation in humans, with translocation assayed as the detection of endotoxin in extraintestinal sites

	Clinical condition			No. of patients with a positive result		
Reference	Test patients	Controls	Site assayed for endotoxin	Test patients	Controls	Lower limit of positivity (pg/ml)
Moore *et al.*[91]	Trauma (≤48 h post injury)	None	Peripheral blood	0 of 20	—	Not reported
		None	Portal blood	0 of 20	—	Not reported
van Goor *et al.*[98]	Critically ill organ donors	None	Peripheral blood	4 of 21	—	>5
			Portal blood	2 of 21	—	>5
			Abdominal fluid	9 of 17	—	>5
Hoch *et al.*[99]	Trauma (≤2 h post injury)	Healthy	Peripheral blood	0 of 30	0 of 6	1
Endo *et al.*[100]	Haemorrhagic shock	Healthy	Peripheral blood	5 of 29	0 of 20	9·8
Roumen *et al.*[101]	Haemorrhagic shock	None	Arterial blood	7 of 11	—	12·5
Roumen *et al.*[101]	Aortic cross-clamp	None	Arterial blood	4 of 5	—	12·5
Shou *et al*[103]	Cardiac bypass (no SDD)	Cardiac bypass (with SDD)	Peripheral blood*	18 of 40	4 of 40	>5

SDD, selective digestive decontamination. *Assayed 4 h after surgery

from sepsis due to a Gram-negative pancreatic infection. There was a significant reduction in the incidence of Gram-negative pancreatic infection in patients who had verified sterile pancreatitis at the time of randomization. This supports the hypothesis that bacterial translocation does actually occur. However, the observation that an equal number of patients developed and died from MOF in the absence of an infective focus does not support a causal relation between bacterial translocation and MOF in this setting.

In 1993, a meta-analysis was conducted of 22 randomized controlled trials of SDD in patients admitted to intensive care units, encompassing a total of 4142 patients[118]. The results of this analysis indicate that a study designed to assess the benefit of SDD in the intensive care setting would require the inclusion of at least 2000 patients. Presently available data clearly fall far short of the statistical power needed to allow definite conclusions.

Another problem with the interpretation of the data derived from SDD studies is that most studies have not determined, by surveillance cultures from the digestive tract, whether or not the gut was actually decontaminated. For example, faecal cultures from patients receiving SDD before elective liver transplantation contained Gram-negative bacteria up to the ninth postoperative day. This may explain why systemic endotoxaemia in these patients was not reduced significantly compared with that in controls[124].

Several clinical trials have been performed with the objective of reducing mortality by binding and neutralizing endotoxin[125–129]. Antiendotoxin antibodies and endotoxin neutralizing peptides have been used. Antiendotoxin treatment of patients with Gram-negative sepsis was reported to reduce mortality significantly[125–127,129], but these results have been criticized[130,131] and could not be confirmed in a more recent study[128]. The negative results may be due to the fact that the antibodies used bound to endotoxin but did not completely neutralize its toxic effects[130,132]. However, considering the most recent theories on the development of MOF[18,19], it seems possible that not all patients benefit from treatment with antibodies against endotoxin (or TNF-α[133] or antagonists of IL-1[134]) because some individuals may be 'immunoparalysed' owing to an excessive secondary anti-inflammatory response.

Endpoints used in human studies

Analogous to the situation of animal experiments, in human studies bacterial translocation has been assessed by culturing mesenteric lymph nodes, or portal and peripheral blood. However, although migration of bacteria and endotoxin via the thoracic duct has been demonstrated in some animal studies[135–137], in humans the lymphatic route of translocation beyond the mesenteric lymph nodes has not been studied in detail. So, to evaluate the occurrence of translocation and its relation to MOF more completely, the thoracic duct lymph concentrations of bacteria, endotoxin and cytokines should also be investigated.

As a second measure, intestinal permeability changes have been used to provide (indirect) evidence for translocation. This hypothesis assumes that a relationship between translocation and intestinal permeability exists, which would occur in critically ill patients. Increased intestinal permeability has indeed been detected in patients with burns[138–140] and following cardiopulmonary bypass[141]. Gut permeability was also studied in those with trauma, with and without MOF[142,143], using healthy volunteers as controls. Although the permeability was significantly increased in all trauma patients compared with healthy volunteers, there was no difference between patients with or without MOF[142]. Roumen and co-workers[144] also showed that there was no relationship between increased permeability and MOF score in patients with severe trauma and haemorrhagic shock. Nor was there any difference in permeability in patients with and without infection. Although measured only in peripheral blood, no endotoxaemia was observed. These data suggest that increased permeability and subsequently infective complications are, at least partly, independent phenomena.

In humans, data on mucosal injury and mucosal atrophy are hard to obtain. One study measured villus height of small bowel biopsies in 58 general surgical patients requiring laparotomy and failed to demonstrate a significant difference between patients with and without bacterial translocation[145].

Role of bacterial translocation in the pathogenesis of multiple organ failure

In the current literature it is increasingly hypothesized that patients may develop MOF through a range of clinical responses. It is proposed, at one extreme, that a massive systemic proinflammatory reaction develops early after the initial insult and that affected patients often die from profound shock within a few days[10,16–19]. In such cases, bacterial translocation seems to have no role in the pathogenesis of MOF. Other, less severely injured, patients are thought to be prone to develop MOF several days or more after the original insult[19]. It is argued that this is caused either by an ongoing systemic pro-inflammatory response or by immunoparalysis, due to an excessive compensatory anti-inflammatory response or to an imbalance between the proinflammatory and anti-inflammatory responses[18,19]. Translocation has been suggested as inducing, perpetuating or intensifying this continuous inflammatory state, as endotoxin is especially known to induce the release of both proinflammatory and anti-inflammatory cytokines[146]. Substantial evidence derived from animal experiments has revealed that an ischaemia–reperfusion insult to one organ may result in dysfunction of a remote organ, especially the lung[36–39]. Trauma and thermal injury are often accompanied by hypovolaemia and so make the patient susceptible to ischaemia–reperfusion injury. In thermal injury and endotoxaemic shock models, a diminished blood flow to the mucosa and submucosa of the jejunum, distal ileum and colon has been demonstrated[33,34,107], whereas flow to other organs was preserved[107]. Therefore, ischaemia–reperfusion injury of the gut is probably a pathway common to shock, trauma and thermal injury[147].

Owing to the countercurrent oxygen exchange mechanism in intestinal villi[148], the oxygen tension at the tip of a villus is much lower than that in arterial blood and, as a consequence, epithelial cell injury may readily develop when the oxygenation of tissues is diminished. It remains to be established during ischaemia–reperfusion injury of the gut whether the epithelial cells or the endothelial cells are initially damaged, or whether this damage occurs concomitantly. Ischaemia of the gut may lead to intestinal epithelial cell injury, which could cause bacterial translocation and subsequently generalized endothelial cell activation and distant organ tissue injury. Alternatively, ischaemia–reperfusion injury might directly induce endothelial cell activation, resulting in local tissue injury. In this way, activation of the intestinal endothelial cells may induce injury of the intestinal epithelium, followed by translocation, which may in turn cause generalized endothelial cell activation and finally distant organ tissue injury. Hence, when evaluating bacterial translocation as a causative factor in MOF in the absence of an infective focus, the type of initiating event and the period of time after which MOF develops should be taken into account. Only scant data on this last issue are available in studies relating translocation to MOF[11], and it remains unknown whether translocation is the initiating event, due to epithelial cell injury, or whether it occurs in addition to primary endothelial cell injury.

Conclusions

The available evidence suggests a role for bacterial translocation in the pathogenesis of MOF. Although most data on translocation have been derived from animal studies, convincing evidence has been provided that translocation may occur in humans during various disease processes. However, despite considerable research effort, it remains to be determined whether a causal relationship exists between translocation and MOF under these circumstances. Therefore, the question of whether translocation is a cause or an epiphenomenon of MOF cannot yet be answered unequivocally.

In classical microbiology, Koch's postulates are tested to prove a causal connection between a hypothesized pathogen and a disease state. These three postulates have all been examined. First, gut-derived bacteria or endotoxin have been searched for in patients with MOF without an infective focus, but rarely found. Second, it has been determined whether exposure to endotoxin might mimic the clinical picture of MOF; the concentration of circulating proinflammatory cytokines measured within hours of endotoxin infusion in healthy volunteers was comparable to that in severely ill patients[9,99,100–102,149], but the clinical picture was not. The most severe clinical symptoms described are those consistent with severe influenza-like symptoms[9,150–152]. Finally, it has been investigated whether it is possible to eliminate the potential pathogens and thereby to attenuate or, ideally, resolve the clinical picture. To date this has not been achieved. It may be stated, therefore, that the application of Koch's postulates does not provide conclusive evidence of a causal role for bacterial translocation in the development of MOF, perhaps as a consequence of the (hypothesized) multifactorial origin of MOF. Currently, it is argued that patients may develop MOF via a range of clinical responses. At one extreme, a massive systemic proinflammatory reaction may develop after the initial insult and affected patients often die from profound shock within a few days. In such cases, translocation seems to have no role in the pathogenesis of MOF. Other, less severely injured, patients are thought to be prone to develop MOF several days or more after the original insult. Most recently, it has been argued that this is caused by an ongoing systemic proinflammatory response or by 'immunoparalysis', due to an excessive compensatory anti-inflammatory response, or by an imbalance between the proinflammatory and anti-inflammatory responses. Bacterial translocation has been suggested as inducing, perpetuating or intensifying this continuous inflammatory state.

Future clinical studies investigating the relationship between bacterial translocation and MOF should take into account the timing of MOF in order to interpret the data more accurately. Moreover, experimental studies should be performed in which the role of the liver and lung in modulating an inflammatory response is investigated; permeability changes of the colon and the lymphatic route of bacterial translocation beyond the mesenteric lymph nodes also require further study.

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Review

Ileoanal reservoir dysfunction: a problem-solving approach

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Background Many technical difficulties of the ileoanal reservoir operation have been overcome, allowing acceptable morbidity in the hands of both the frequent and less frequent operator. However, a minority of patients have persistently unsatisfactory pouch function, which can be a difficult problem to manage.

Methods A Medline search was carried out to identify relevant papers published from November 1996 to January 1978. For clinical information more emphasis was given to recent publications with larger numbers. Where appropriate, information from other sources and some local data were included.

Results Most patients empty the pouch four to eight times a day with perfect continence and no urgency, and are considered to have acceptable function with which they are satisfied. Patients who have poor function beyond an easily treated episode of pouchitis require the expertise of a multidisciplinary team offering some understanding of the anatomy, physiology and pathology of the gastrointestinal tract in general and of the ileal reservoir in particular. A thorough and persistent approach to difficult cases is often rewarded with a good outcome, with the exception of problems arising from postoperative sepsis. The temptation to use pouchitis as a waste-basket diagnosis for poorly understood dysfunction should be avoided. Problems causing poor function may originate in the pouch (including pelvic sepsis), the pouch outlet, or the small bowel above the pouch, and these areas need to be considered in each case.

Conclusion To optimize the benefits of restorative pouch surgery, both patients and physicians need to understand aspects of fine tuning of pouch function, including diet, medication and lifestyle. In managing ileoanal reservoir dysfunction the temptation to procrastinate should be resisted, an approach that is systematic and sympathetic should be adopted.

With the rapidly growing number of patients having ileoanal reservoirs, there can be few surgeons and gastroenterologists with an interest in colorectal disease who have not encountered a reservoir that does not work very well. Technical refinements to restorative proctocolectomy have reduced perioperative morbidity, leading to a mortality rate of 1 per cent and a 30-day complication rate of 20–30 per cent[1]. Such results appear to be obtainable by both the frequent and less frequent operator[2], albeit with some selection bias. In large series from tertiary referral centres, 90 per cent of patients report an excellent quality of life[1,3] soon after surgery and only a few have significant problems with function. However, it is dispiriting for both surgeon and patient to have successfully negotiated a series of major operations only to find that quality of life is still below par because of a poorly functioning ileal pouch. Poor function may be short lived and easily remediable, but this is not always the case. This paper reviews the literature on pouch dysfunction and draws on the authors' own experience, with the aim of promoting an effective management approach for patients with poor reservoir function.

Defining dysfunction

Pouch function may vary greatly from one person to another and from day to day. It may depend on fluid intake, and the timing and composition of meals. What falls outside the bounds of acceptable pouch function clearly represents dysfunction, but within the bounds of acceptable pouch function an individual may still have the opportunity for significant improvement in function. The goal is always to achieve the best function on an individual basis.

Most patients with a pouch empty it four to eight times a day[1,4–7] and, unless there are significant problems, they should not need to do this more frequently. This corresponds to evacuating a stool volume of 500–700 ml per day[8]. Pouch evacuation should be achieved without urgency; the patient should be able to defer emptying for 20–30 min or longer. Many patients do not need to empty the pouch during the hours of sleep, but the need to empty it once or twice during the night is acceptable. On passing stool the pouch should empty spontaneously without pain. For the majority continence is perfect[9,10], and 60 per cent can discriminate and pass flatus without fear of soiling. Double stapling the pouch to the top of the anal canal results in minor nocturnal leakage in about 10 per cent of patients[10–13], and this value rises to 20–40 per cent[14–19] in those who have had a mucosectomy and hand-sewn pouch–anal anastomosis. Social convenience, timing of medication and diet affect the pattern of emptying. Function outside these limits may broadly be considered pouch dysfunction. *Table 1* lists the symptoms that may be attributed to aspects of pouch dysfunction.

Investigation of the problem pouch

A clinical history about pouch function should include questions on frequency of emptying by day and night,

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Table 1 Features that may be associated with pouch dysfunction

Colicky abdominal pain
Pelvic pain
Perineal pain
Watery motions
Blood in motions
Excess frequency of emptying
Pain on evacuation
Incomplete emptying of pouch
Urgency
Anal irritation and pain
Leakage of stool
Perineal discharge from fistula *in ano*
Vaginal discharge (flatus or faeces)
Lethargy, fever, rigors

continence, discrimination of pouch contents, use of antidiarrhoeal medication, diet and eating pattern and, in the first 6–12 months after surgery, questions about bladder and sexual function. Examination of the pouch should include a thorough digital examination seeking any fistulas, fissures, skin excoriation, anastomotic stenosis, mucosal prolapse[20], induration or tenderness of the anastomosis, and assessment of the height of the anastomosis. Pouchoscopy with a paediatric sigmoidoscope allows assessment of the pouch mucosa and some impression of pouch volume is also possible. Biopsies should be taken from the anterior and posterior walls of the pouch as inflammation can vary in different regions[21]. A protoscope should then be used to inspect and biopsy the columnar cuff[22] (columnar epithelium that starts in the mid-anal canal and extends to the pouch–anal anastomosis), again noting the presence of any inflammation. If it is impossible to carry out such an initial assessment in the outpatient clinic because of discomfort, an examination under sedation or under anaesthesia is required. Examination under anaesthesia is usually needed to assess all but minor perianal and anastomotic problems. If further elucidation of pelvic or perianal sepsis is required, magnetic resonance imaging (MRI) is the investigation of choice and is more sensitive than endoanal ultrasonography[23,24].

The pouch is rarely empty in the outpatient clinic, making a thorough examination with a rigid scope difficult. If matters are not resolved simply after initial assessment there should be a low threshold for flexible endoscopy after an overnight fast and an enema. This should include examination of the pre-pouch ileum as well as the pouch itself, with multiple biopsy specimens from both areas.

If there is pouch frequency in the absence of any obvious cause, maximum tolerated pouch volume may be measured in an anorectal physiology unit. Concerns about sphincter function should be investigated with anal physiology studies and ultrasonography. Symptoms suggesting poor pouch emptying, which include excess pouch emptying frequency, may prompt an evacuation study[25–29] using scintigraphy. Between 50 and 75 per cent of the radiolabelled paste should be emptied on any evacuation. If there is no clear cause of persisting poor function after initial investigations and every endeavour has been made to tune pouch function, it is appropriate to investigate the proximal small bowel. Such investigation may include endoscopy, measurement of stool volume and barium studies.

Causes of dysfunction

Causes of pouch dysfunction are related to one or more of three sites: the pouch itself (including pelvic sepsis), the pre-pouch small bowel, and the pouch outlet. Problems in one region will often cause secondary problems in another.

The pouch

Pouchitis. Pouchitis is probably the commonest problem affecting pouches and in most cases it is straightforward to treat; it occurs in 7–45 per cent of pouches[30]. This wide variation in incidence is largely due to historically loose diagnostic criteria but these have now been tightened resulting in reported rates of pouchitis in larger series of 15–25 per cent[1,27,31–33]. Shepherd *et al.*[34] have proposed that a diagnosis of pouchitis should require the triad of: (1) clinical symptoms including diarrhoea (often with blood), fever, malaise, anorexia and occasionally extraintestinal manifestations; (2) endoscopic evidence of acute inflammation; and (3) histological evidence of acute inflammation with a combined acute and chronic histological score of 9–12. Sandborn *et al.*[35] have developed a Pouch Disease Activity Index that is based on scoring each of the three elements of the diagnostic triad. This index requires less rigorous histological criteria than those proposed by Shepherd and co-workers but its proponents argue that this appropriately includes some cases of pouchitis that would otherwise be excluded[36]. Only half who present with a history suggesting pouchitis fulfil the criteria proposed by Shepherd *et al.*[34,37]. Much of this disparity may result from the logistical difficulty of carrying out endoscopy and biopsy at the onset of symptoms, and the patchy nature of inflammation within pouches[38]. The latter means that, unless a pouch is completely empty and examined with a flexible endoscope, inflamed areas may be missed and not biopsied, with an inevitable failure to recognize the diagnostic triad. In a recent paper from the United States, Hurst *et al.*[39] proposed that a symptom complex suggesting pouchitis and response to 7 days of antibiotic therapy are sufficient criteria to support a diagnosis of pouchitis. This is, however, unsatisfactory; it disregards other causes of aberration in pouch function, the placebo effect of medication, and the fact that many patients may have improved without antibiotics or because of therapeutic effects that are not related to pouchitis. Hurst *et al.*[39] claimed that the criteria for the diagnosis of pouchitis are controversial and yet to be defined, but this ignores the view from the other side of the Atlantic which holds that the diagnostic criteria and definition of pouchitis are clear[37,40–43]. Difficulty in confirming a diagnosis of pouchitis is not due to the criteria themselves excluding cases, but to the practical problems of obtaining the appropriate biopsies at the right time. In practice many patients receive empirical treatment. If progress in understanding pouchitis is to be made in an evidence-based manner, it is important to seek and apply the accepted criteria to diagnose the condition; this includes histological appearance.

Recurrent pouchitis is likely to begin in the first 6 months of pouch function[44]. Occasionally there may even be troublesome 'pouchitis' in the reservoir before the ileostomy is closed. Defunction pouchitis is probably an entirely separate entity similar to the changes of 'diversion colitis' seen in the defunctioned rectum in ulcerative colitis[45]. Patients with pouchitis seem to fall into two groups: a majority (75 per cent) have a few isolated attacks but otherwise no problems, and a minority (25 per cent) develop chronic pouchitis with frequent exacerbations[1,44] requiring almost continuous treatment. Whether the aetiology is the same in both groups is not clear. It is possible that genetic[46] or environmental[47] factors, such as smoking, may be relevant.

The aetiology of pouchitis, as of inflammatory bowel disease, is unknown. Stasis in the pouch allows the growth of anaerobic flora, producing concentrations intermediate between those in an end-ileostomy and those in the colon. However, despite pouchitis responding to metronidazole, there is no correlation between histological inflammation and bacterial count in the pouch[48,49]. The altered bacterial flora produce concentrations of short-chain fatty acids (SCFAs) similar to those in the colon[48]. SCFA levels have been reported to be lower in patients with pouchitis[49] but this may be dilutional or an epiphenomenon[36]; treating pouchitis with SCFAs has not proven useful[50]. Because of the alteration in bacterial flora there is deconjugation and dehydroxylation of bile acids that may be toxic to the mucosa, but the levels of these do not seem to correlate with pouchitis, and cholestyramine is of no benefit in treating pouchitis[36,43]. All these changes in the luminal content that is in contact with the small bowel mucosa of the pouch, while not the cause of pouchitis[51] are probably responsible for the colonic phenotypic change observed in the pouch mucosa. The currently favoured hypothesis for the aetiology of pouchitis supposes that colonic phenotypic change in the pouch mucosa exposes the mucosa to an immunological attack analogous to the process that produces ulcerative colitis. This fits with the observation that pouchitis is rarely if ever seen in patients who have a pouch because of familial adenomatous polyposis. In addition, attacks are associated with similar extraintestinal manifestations to those found in patients with ulcerative colitis[36,43,52]; there is also a higher incidence of sclerosing cholangitis and positive staining for perinuclear antineutrophil cytoplasmic antibody in patients with chronic pouchitis[53]. Uncommonly, ischaemia or infection in the pouch may fulfil the diagnostic criteria for pouchitis, but these are separate diseases from idiopathic pouchitis. Stool cultures should be taken to exclude infection. The most common organisms are *Campylobacter*, *Salmonella* and *Clostridium difficile*[11].

Proposed treatment of pouchitis is outlined in *Fig. 1*. If pouchitis is confirmed or suspected, symptoms usually settle with a 7–10-day course of metronidazole, ciprofloxacin or co-amoxiclav. Episodes of pouchitis may rarely settle spontaneously. Antibiotic therapy is largely empirical, although one recent trial has shown metronidazole to be better than placebo for chronic pouchitis[54]. The mechanism of action of antibiotics is not clear. It may involve a secondary effect of alteration of the bacterial flora in the gut, perhaps by decreasing the pH in the pouch[55]. To control symptoms in patients with chronic severe pouchitis antibiotics may be needed for 1 or 2 weeks in every month or even continuously, rotating the type of antibiotic. Care should be taken when using long-term metronidazole because of the risk of peripheral neuropathy. If antibiotics are not effective, strategies used for treating ulcerative colitis may be tried, such as 5-aminosalicylic acid or corticosteroids, either topically or orally. There are anecdotal reports of treatment with SCFAs, cholestyramine, bile salts and nicotine patches, but these agents remain experimental. If there is any concern about suboptimal pouch emptying and stasis causing pouchitis, a regimen of pouch emptying with a Medena catheter at 2-h intervals may be worthwhile. If the problem is severe and refractory to treatment, it may be worth defunctioning the pouch for a period, as a final attempt to achieve resolution before resorting to pouch excision, which is required in 3 per cent of those with pouchitis[1].

Pouch volume A compliant pouch of good volume is essential for good function[56–59]. A small stiff pouch usually leads to frequency and urgency of pouch evacuation. Different pouch designs (S, W and J) and different lengths of small bowel may be used, but these do not result in a pouch with significantly larger maximum tolerated volume or decreased frequency[27,60,61], as might be predicted by mathematical models[62]. Other factors, not

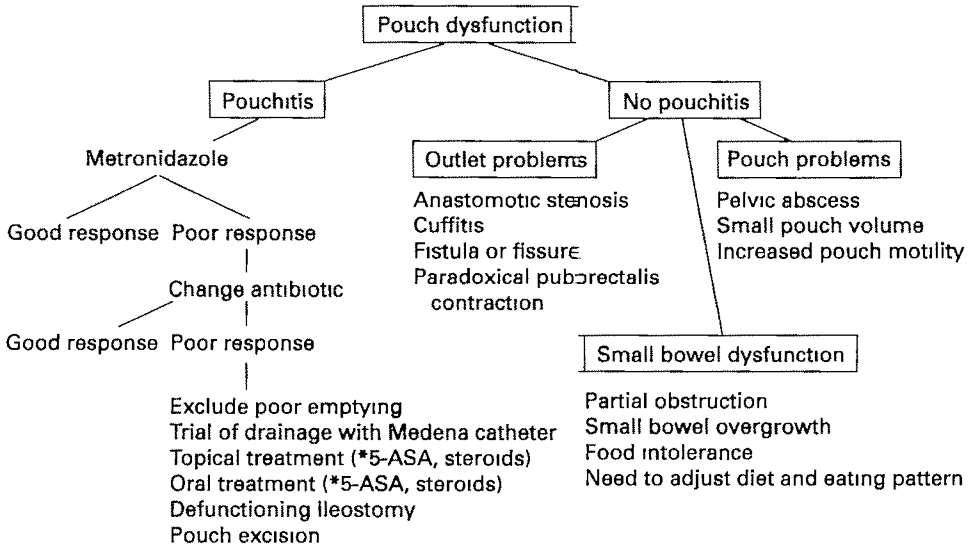

Fig. 1 Algorithm for pouch dysfunction and the treatment of pouchitis *5-ASA, 5-aminosalicylic acid

always well understood, may lead to large variations in the pouch volume[56]. A pouch should generally have a volume between 200 and 450 ml[27,56,63,64]. Pouch volume increases over the first year of function and this is associated with a decrease in the frequency of emptying[65,66]. The most significant adverse factor affecting volume is pelvic sepsis, which causes scarring and fibrosis around the pouch. An impression of volume and compliance may be obtained at endoscopy but, if there is concern, the volume should be assessed by anorectal physiology using a balloon. If a pouch has a volume of 150 ml or less and there is no other obvious cause for unacceptable function, pouch excision or revisional surgery should be considered. It is possible to augment pouch volume by incorporating an additional loop of small bowel[67].

Pelvic abscess. About 5–12 per cent of patients will develop a pelvic abscess[1,5,68,69] and, significantly, half of these will occur more than 30 days after operation[1]. A pelvic abscess is usually accompanied by systemic manifestations as well as symptoms of pouch dysfunction. Pelvic sepsis should always be considered as a cause of pouch dysfunction. There may be pelvic pain, especially on emptying the pouch, and frequency or urgency that may precipitate minor incontinence. The pouch mucosa is likely to be secondarily inflamed. Any suspicion of pelvic sepsis, particularly in the postoperative period, must be aggressively pursued to minimize the risk of compromising long-term pouch function[70]. This includes examination under anaesthesia, computed tomography, MRI (useful for detecting small occult collections), percutaneous or open drainage of collections, identification of any leaks, and often a defunctioning ileostomy.

Pouch motility. Increased motor activity in the pouch correlates with poorer function[71] and nocturnal leakage[72,73] when pouch pressure exceeds anal canal pressure. The generation of large-amplitude propulsive waves at lower volumes during pouch filling is associated with increased frequency of evacuation[74]. Continent patients have nocturnal pouch motor activity similar to that of the normal rectum[74,75]. Loperamide may decrease pouch activity and improve pouch function by acting locally and, as systemic absorption is negligible, it may be used in combination with oral loperamide[76].

Pouch outlet problems

Paradoxical puborectalis contraction. This causes difficulty in evacuating in a small proportion of patients who complain of having to use excessive abdominal prssure to empty the pouch. Most can be usefully helped with biofeedback[77].

Pouch outlet obstruction and ileal pouch–anal anastomotic stricture. Pouch outlet obstruction presents as difficulty with emptying. This may include incomplete and frequent emptying, anal pain, an angled stream of stool on evacuation, and pelvic discomfort. If severe, the consequences of what is effectively a partial small bowel obstruction are seen, including colicky abdominal pain, a high volume of loose stool, pouchitis and pre-pouch ileitis from stasis. Stenosis from healing of the ileal pouch–anal anastomosis is the commonest cause of stenosis but scarring from perianal sepsis is a more serious problem. Anastomotic stenosis occurs in 9–19 per cent of patients and may be more frequent after stapling the pouch–anal anastomosis[1,4,78]. The stenosis is usually diaphragm-like and most can be dilated in the outpatient clinic; about 20 per cent require general anaesthesia. Dilatation may need to be repeated several times over 6–18 months after pouch formation, but stenosis is rarely a long-term problem. If severe and persistent it is possible to deal with it by excision of the anastomosis and pouch advancement, either at laparotomy or using a per anal approach[67,79]. Rarely a pouch may develop prolapse and this can be treated by 'pouchpexy'[80].

Cuffitis The majority of pouches are now constructed using a double stapling technique for the pouch–anal anastomosis. In practice this involves retention of a cuff of columnar mucosa 1·5–3 cm in length[22]. Initial work on operative specimens suggested that the anal canal was involved in ulcerative colitis in the same manner as the colon[81] and the long-term consequences of retaining the columnar cuff are not yet known. In the shorter term, Lavery *et al.*[82] from the Cleveland Clinic studied 217 patients with a mean follow-up of 30 months. Inflammation ranging from mild to severe was noted in 82 per cent of anal canal biopsies. Symptomatic inflammation that correlated with both endoscopic and histological inflammation was found in 14·7 per cent of cases. Symptoms in the nine patients who had no concurrent pouchitis included urgency, pain and bleeding which responded to topical steroids. In those with pouchitis, all symptoms settled with treatment directed at both the pouchitis and anal canal inflammation. The present authors have treated two cases of persistent cuffitis successfully with lignocaine gel, which both relieved the symptoms and produced a rapid resolution of endoscopic and histological inflammation, perhaps due to the anti-inflammatory properties of lignocaine. Symptoms do not always settle, however, and Curran and Hill[83] have described three patients who required mucosectomy for ongoing symptoms, one of whom came to pouch excision. If surgical treatment is required, mucosectomy and pouch advancement can yield good results[84]. Careful examination of the columnar cuff requires a proctoscope, and biopsies can be taken without discomfort if obtained from the upper anal canal or from just below the pouch–anal anastomosis. If symptomatic cuffitis is confirmed on endoscopy and histology, a trial of steroid suppositories or enemas is warranted.

Pouch–vaginal and pouch–perineal fistula. These present with flatus, an unusual discharge or stool passing through the vagina or perineum, and may be associated with symptoms of pain, urgency and leakage. Pouch–vaginal fistula occurs in 4–10 per cent of women[1,85–87] and may present many years after pouch formation[88]. While the symptoms may be clearcut, identification of the fistula is not always easy and an examination under anaesthesia is required for assessment. Most fistulas are low and track from the level of the pouch–anal anastomosis, or close to it[86,87], to the lower vagina. They may be considered as three types: those that arise soon after surgery and are anastomotic complications, those that arise late after operation where the aetiology is not clear, and those that are due to Crohn's disease. Management options include setons, pouch or vaginal advancement flaps, and excision of the pouch–anal anastomosis with advancement of the pouch[79,85,87]. Limited data suggest that results are good for early postoperative fistulas but up to half the patients in the other categories may lose the pouch[85–87]. Pouch–

perineal fistula seems to be a less common problem for which similar treatment options exist; three cases of successful treatment with a cutting seton fistulotomy have been described[86].

Poor sphincter function and frequent emptying. Although there may be preservation of normal sphincter physiology and continence after pouch formation[9], function may vary; there is often a significant drop in resting anal pressure, which is usually greater in patients who had a mucosectomy and hand-sewn anastomosis[13,22,89]. This drop in resting anal pressure is responsible for minor leakage in 10–40 per cent of cases. Leakage rates decrease in the first few years after pouch formation[5]. Patients with poorer sphincter function complain of minor leakage, particularly during sleep when resting pressures are lower[90] and the external sphincter is not so readily responsive. Sphincter integrity may be investigated with anorectal physiology studies and endoanal ultrasonography. All parous women and those with a history of anorectal problems or any abnormality on examination should have a preoperative evaluation using these techniques, which should permit correct counselling and aid decision making. They also allow a baseline to be established before operation. If there is poor sphincter function after surgery and there is no remediable problem in the pouch outlet, management is based on optimizing pouch function and stool consistency to enable the sphincter to preserve continence most effectively. Major incontinence related to poor sphincter function occurs in 1–2 per cent[1]. This is usually the result of either inadequate preoperative evaluation of the sphincter, poor operative technique or major septic complications. Most of the affected patients will come to pouch excision and permanent ileostomy. In a few there may be a role for sphincter repair; perhaps in the future more sophisticated sphincter substitutes will be offered.

Anal fissure. Anal fissure may be present in patients with pouches but does not always produce symptoms. Symptomatic treatment with lignocaine jelly is usually successful and a trial of 0·2 per cent glyceryl trinitrate ointment is worth considering[91]. Anal stretch should never be performed, and lateral sphincterotomy should be reserved for exceptional circumstances and considered only if there is a hypertonic sphincter recognized by anorectal physiology studies.

Excoriation of the perianal skin. The perianal skin is susceptible to attack by ileal content, and excoriation can be very distressing. When it occurs a regimen of cleaning and drying the skin and then applying a barrier cream is important. Some food and drinks (e.g. citrus fruits and juices, and spicy foods) make excoriation worse, as do very loose motions. Cholestyramine by mouth may be helpful, implicating bile acids as a provoking factor.

Long efferent limb. The earliest pouches were of an S configuration and many of these could not empty spontaneously because the efferent limb was too long. Some patients happily empty with intermittent catheterization and others have had successful revision to shorten the efferent limb[67,92,93]. This problem is becoming historical as S pouches are now rarely constructed and surgeons are aware that the efferent limb should be very short.

Problems in the small bowel

Most problems arising upstream of the pouch result in frequent loose motions because of the delivery of an increased volume of liquid small bowel content into the pouch. Unless symptoms point specifically to the small bowel, attention is focused elsewhere until other investigations and treatment options have been exhausted. Joint management with a gastroenterologist is important when the small bowel is implicated.

Adhesions. Adhesions cause small bowel obstruction in up to 15–30 per cent of patients after a pouch procedure and lead to reoperation in about 5–10 per cent[4,5,69,94,95]. Colicky abdominal pain, borborygmi, distension and diarrhoea may indicate a partial small bowel obstruction and this should be investigated with a small bowel barium enema. Recent work with a hyaluronidase-impregnated methylcellulose membrane shows significant promise in reducing problems from adhesions[96].

Small bowel bacterial overgrowth. Increased stool frequency and stool volume in patients without pouchitis has been correlated with small bowel bacterial overgrowth, as measured by increased numbers of aerobic and anaerobic organisms cultured from jejunal aspirates[97]. This may explain why some patients with poor function improve when treated with antibiotics for presumed pouchitis which fails to be confirmed by subsequent histological examination. Bacterial overgrowth may be caused by a partial functional obstruction due to decreased jejunal motility from the exaggerated ileal brake mechanism triggered by stasis of nutrients in the pouch[98–100]. Treatment of small bowel overgrowth is usually empirical and a therapeutic trial of antibiotics is usual. Diagnosis may be confirmed by culturing abnormal numbers of bacteria from small bowel aspirate. The lactulose breath test is difficult to interpret in patients who have had excisional intestinal surgery and should not be used. Mechanical obstruction may also cause overgrowth of small bowel flora, and obstruction should be excluded in the course of investigation.

Food intolerance or allergy. Food intolerance is another potential cause of unexplained frequent loose motions. If this is suspected the assistance of a gastroenterologist and dietician may be useful; a trial of an exclusion diet should be undertaken. Pre-existing hypolactasia, which was asymptomatic in the presence of a colon, may become apparent with the loss of colonic absorption.

Small bowel motility and transit. One study has shown a significant increase in the number of small bowel migrating motor complexes in patients with increased frequency of pouch evacuation, but the reservoir volume in these patients was also smaller[58]. A dual isotope technique used to study gastrointestinal transit showed no relationship between rate of transit and frequency of pouch emptying[101], suggesting that the increase in manometric activity does not correspond to more rapid transit. Occasionally, small bowel manometry exhibits the pattern found in obstruction, supporting the concept that pouches may produce a functional obstruction by the ileal brake mechanism[102]. In the terminal ileum of patients having a restorative proctocolectomy for ulcerative colitis, there may be defective nitric oxide-mediated relaxation in one-third of patients and a complete absence of enteric neuronal relaxation in a further third. Abnormalities like this in the distal small bowel–pouch unit may explain some of the poorly understood variability in pouch function and volume[103].

Pre-pouch ileitis. This has been described, albeit rather sketchily, and is probably related to stasis in the afferent limb from partial obstruction to this limb as it enters the pouch. It may also be due to the continuation of significant pouchitis, particularly if there is a degree of mechanical or functional obstruction in the pouch. The diagnosis is made on flexible sigmoidoscopy with biopsy. If it does not settle with antibiotics, relief of any obstruction and further treatment with mesalazine or steroids, it may respond to a temporary defunctioning ileostomy.

Crohn's disease. Up to 5–7 per cent of patients[1,69] in large pouch series eventually have a diagnosis of Crohn's disease. This underlines the need for a very careful clinical and pathological evaluation of each case before surgery. Crohn's disease in the pouch resembles Crohn's disease elsewhere in the gut, but care is needed in interpreting pouch biopsies as patchy inflammation with granulomas can be a feature of pouch histology in the absence of Crohn's pathology[21,104]. It is pathology without the pouch, in the form of perianal or small bowel Crohn's disease, that allows the diagnosis to be made. About 25–30 per cent of affected patients will lose the pouch[1,105], a finding at odds with a recent controversial series reported in the *Lancet*[106] supporting restorative proctocolectomy for selected patients with Crohn's colitis and describing a pouch loss rate of only 10 per cent.

Fine tuning of pouch function

This is the optimization of pouch function once other problems have been treated or excluded. Much of this involves optimizing stool consistency and volume. A porridge-like consistency is probably ideal for most, as this allows easy emptying and is less challenging to the sphincter than more liquid stool. Diet has a definite effect on pouch function in terms of consistency and flatus; about 40 per cent of patients consider they make dietary restrictions[1,107]. This varies from patient to patient but some common foods and their typical effects are listed in *Table 2* Patients can use such a list as a guide but they will need to determine for themselves their optimal diet for best pouch function and balance this against what they wish to eat. Timing and size of meals will also affect how and when the pouch empties and each patient needs to find his or her own personal pattern.

Medication is the other important tool for improving pouch function; 20 per cent of patients take regular and 50 per cent occasional antidiarrhoeal medication[1,108]. The mainstay is loperamide, which causes increased absorption of water by decreasing small bowel motility and reduces stool volume, an important determinant of pouch frequency[8], by about 30 per cent[109]. Furthermore, loperamide increases resting anal pressure through an effect on the internal sphincter[110]. Combined, these actions decrease pouch frequency and minor leakage. The patient must adjust the dose and timing of the medication and may take up to eight 2-mg tablets in 24 h. There seem to be few ill effects from lifelong use of loperamide. Codeine may be used concurrently but, if the pouch content becomes too thick, difficulty in emptying the pouch will ensue. Up to 20 per cent of patients benefit from bulking agents[6] such as ispaghula husk or methylcellulose to thicken the stool. Oral calcium supplements of 1·5 g per day have been reported to decrease pouch frequency[111] but they are not widely used.

Table 2 Foods reported by patients that may affect pouch function

Increase output	Decrease and thicken output	Increase wind	May obstruct bowel and pouch inlet or outlet
Beans Beer Caffeinated beverages Chocolate Leafy green vegetables Raw fruits and vegetables Spicy foods Wholemeal food Cereal Alcohol Citrus fruits and juice	Apple sauce Bananas Boiled rice Cheese Creamy peanut butter Tapioca White bread Potatoes Suet pudding Pasta	Beer Carbonated beverages Dried beans and peas Milk and milk products Onions Cabbage family (cabbage, broccoli, sprouts)	Mushrooms Sweetcorn Potato skins Nuts Tomato skins Raw fruit skins Celery strings

Unpublished data from a survey of 62 patients with ileoanal pouches at Oxford, by Catherine Meadows, stomatherapist

Summary

A poorly functioning pouch can cause distress, anxiety and disappointment for patients, but a thorough, persistent and sympathetic approach to the problem will produce acceptable pouch function for the vast majority. Problems that may cause pouch dysfunction are summarized in *Fig. 1*.

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Association of Surgeons of Great Britain and Ireland

The Annual Scientific Meeting of the Association of Surgeons of Great Britain and Ireland was held in Bournemouth on 9–11 April 1997 under the Presidency of Professor Sir David Carter. The abstracts of the oral and poster presentations of the original work presented at the meeting have previously been published in a BJS Supplement which accompanied the May 1997 issue of the Journal. The articles that follow in the present issue describe work presented at the Bournemouth meeting; these are full papers which have been accepted for publication after peer review by the Journal's referees.

John Murie
Joint Editor

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Duplex assessment of run-off before femorocrural reconstruction

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Background This study was a prospective evaluation of colour duplex imaging for the assessment of distal run-off before femorocrural reconstruction.

Methods Patients with critical ischaemia who required a distal bypass underwent preoperative run-off assessments using dependent Doppler, arteriography and duplex imaging by a vascular surgeon, radiologist and technologist respectively; each was blinded to the findings of the others. Preoperative data were compared with intraoperative clinical findings and completion flow studies/arteriograms.

Results Forty-three consecutive patients (33 men, ten women; mean age 78 (range 53–95) years; 12 diabetic) undergoing 44 femorocrural reconstructions for critical ischaemia were assessed. The 30-day primary cumulative graft patency for the series was 86 per cent. Dependent Doppler correctly predicted a suitable run-off vessel in 21 limbs but was indeterminate in four and unrecordable in 19. Arteriography correctly predicted a suitable run-off vessel in 32 cases, but was indeterminate in six and failed to demonstrate run-off in three patients. Arteriography suggested an inferior vessel in three cases. Duplex correctly predicted a suitable run-off vessel for all 44 grafts.

Conclusion Duplex imaging is superior to arteriography for preoperative assessment of distal run-off for femorocrural reconstruction.

Femorotibial grafting is an established technique for occlusive vascular disease and the trend has been for bypass on to increasingly distal vessels, including the pedal arteries[1–3]. These procedures are technically demanding and require careful patient selection, detailed preoperative planning and meticulous surgical technique, as well as postoperative surveillance[4]. The quality of the distal vascular run-off is one of the most influential factors with respect to graft outcome; a patent run-off artery and an intact pedal arch are vital[5,6].

Preoperative contrast arteriography has been the mainstay of run-off assessment and the 'gold standard' against which other modalities are compared. Despite modern techniques for enhancing arteriographic visualization, there are limitations. In patients with critical ischaemia and multisegmental disease, preoperative arteriography may underestimate tibial vessel patency by up to 20 per cent and pedal arch integrity by up to 86 per cent[7,8]. To avoid unnecessary amputation, one approach has been direct surgical exposure of individual arteries and on-table arteriography before reconstruction[7–11], with or without resistance measurements[12]. There is a strong case for deciding the optimal run-off vessel before surgery is undertaken and this has stimulated the search for an additional modality to supplement preoperative arteriography.

Doppler insonation, aided by dependency of the affected limb, and pulse-generated run-off measurements have both been advocated[13–16]. They provide a haemodynamic but not anatomical assessment. Magnetic resonance angiography (MRA) can delineate distal run-off vessels even when flow velocities are very slow, but MRA has no functional component and patient tolerance may be a limiting factor[17]. Colour duplex ultrasonographic imaging provides both a functional and anatomical assessment and is well tolerated[18,19].

The objectives of this study were to evaluate prospectively colour duplex imaging for preoperative assessment of tibial and pedal arteries in patients with critical ischaemia, to validate the duplex results with subsequent intraoperative findings and graft outcome, and to compare duplex imaging and preoperative arteriography.

Methods

Between January 1995 and January 1997, all patients with critical ischaemia proceeding to infrapopliteal bypass for limb salvage were studied. Data were collected prospectively and analysed retrospectively. Preoperative run-off assessments were conducted using dependent Doppler, contrast arteriography and colour duplex imaging, carried out by a surgeon, radiologist and vascular technologist respectively, each blinded to the findings of the others. For each modality, the operator was asked to

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recommend the most suitable vessel for siting the distal anastomosis

The distal duplex studies specifically were all carried out by an experienced, accredited vascular technologist (J.K G.), using an ATL (HDI) colour scanner (Advanced Technology Laboratories, Stevenage, UK) and a combination of linear array transducers (L7-4 (4–7 MHz) and L10-5 (5–10 MHz)) to enable visualization of arteries at variable depths, depending on the site being scanned. In practice, scanning commenced at the malleolar level with the patient supine and, on detecting an image or flow signal, scanning was extended into the foot to establish whether there was continuity with the pedal arch, and then up into the calf to determine the proximal extent of patency which was marked on the leg. Occasionally, scanning was conducted with the affected limb dependent over the side of the couch to augment flow signals. Whilst imaging the pedal arch, Roedersheimer's compression test enabled assessment of the integrity of the arch and evaluation of the dominant feeding vessel[20]. Selection of the most suitable run-off vessel for bypass was made on the basis of conventional velocity criteria allowing mapping of stenoses, and colour flow images which reflected anatomical criteria such as calibre, calcification and continuity with the pedal arch.

Before surgery, the most suitable tibial vessel for distal anastomosis and the anatomical approach were selected on the basis of the findings of all three modalities and taking into account availability of vein and the condition of the overlying tissues. At operation, with the preselected vessel exposed, its patency and quality could be assessed. On completion of the anastomosis, on-table arteriography and haemodynamic flow measurements (OpDop 130; Scimed, Bristol, UK) were carried out to confirm patency of run-off (including the pedal arch) and to exclude technical problems.

Statistical analysis

To test agreement between duplex imaging and arteriography, kappa analysis and McNemar's test were applied. Kappa analysis permits an estimation of agreement corrected for chance and McNemar's test is a non-parametric test for two related dichotomous variables, testing for changes in responses using the χ^2 distribution. Life-table analysis was carried out according to the guidelines of the Ad Hoc Committee on Reporting Standards[21].

Results

Forty-three consecutive patients (33 men, ten women; mean age 78 (range 53–95) years; 12 diabetic), undergoing 44 femorocrural reconstructions for critical ischaemia were recruited. Where Doppler signals were detected, absolute ankle pressure measurements were 50 mmHg or less. All the patients had ischaemic pain at rest and 31 had frank ulceration. *Table 1* gives operative details. The 30-day primary cumulative patency and limb salvage rates were 86 (s.e. 5·2; 95 per cent confidence interval (c.i.) 76–96) per cent and 93 (s.e. 3·9; c.i. 85–101) per cent respectively. The primary cumulative patency at 12 months was 76 (s.e. 8·5; c.i. 59–93) per cent. For vein grafts only, the equivalent 30-day and 12-month patencies were 88 (s.e. 5·7; c.i. 77–99) per cent and 77 (s.e. 9·0; c.i. 59–95) per cent, and for polytetrafluoroethylene grafts 82 (s.e. 11·6; c.i. 59–105) per cent and 41 (s.e. 14·0; c.i. 13–69) per cent.

Table 1 Femorocrural graft details ($n = 44$)

Graft type	*n*
Reversed saphenous vein	25
Non-reversed saphenous vein	8
PTFE with vein cuff	11
Run-off vessel	
Anterior tibial	17
Posterior tibial	19
Peroneal	8
Site of distal anastomosis	
Proximal tibial	14
Mid tibial	17
Distal tibial	13

PTFE, polytetrafluoroethylene

With regards to preoperative planning and, specifically, selection of the most suitable calf vessel and siting of the distal anastomosis, duplex imaging was the best and dependent Doppler the least reliable (*Table 2*). Dependent Doppler correctly predicted a suitable run-off vessel in nearly half the patients, but was equivocal in four and failed to detect flow signals altogether in another 19 patients who still went on to have successful bypasses. Contrast arteriography correctly predicted a suitable run-off vessel in 32 patients, but was equivocal in six and failed to delineate run-off in three patients, whilst recommending a suboptimal vessel for bypass in another three. Colour duplex imaging correctly predicted a suitable run-off vessel in all 44 critically ischaemic limbs, as substantiated by the operative findings and completion studies.

To compare preoperative arteriography and duplex directly, each tibial artery was scored, with 0 denoting an occluded artery, 1 a patent artery but an occluded arch, and 2 a patent vessel continuous with the pedal arch. A maximum score of 6 was possible for each patient. Of the 132 possible tibial segments, duplex imaging detected more patent vessels overall and, moreover, detected 15 vessels continuous with a pedal arch that arteriography failed to delineate (*Table 3*). According to kappa analysis,

Table 2 Comparative performance of dependent Doppler, contrast arteriography and duplex scanning in the preoperative detection and selection of a suitable run-off vessel as verified by intraoperative findings and follow-up

	Dependent Doppler	Arteriography	Duplex
Suitable vessel selected	21 (48)	32 (72)	44 (100)
Equivocal	4 (9)	6 (14)	0
Failed	19 (43)	3 (7)	0
Suboptimal vessel selected	0	3 (7)	0

Values in parentheses are percentages

Table 3 Agreement between preoperative arteriography and duplex imaging with regard to number of patent tibial vessels detected

	Duplex assessment		
	0	1	2
Arteriography			
0	55	9	5
1	3	13	10
2	1	0	36

A total of 132 segments were assessed, and scored as. 0, occluded vessel; 1, patent vessel but discontinuous with pedal arch; 2, patent vessel continuous with a patent pedal arch kappa 0·72; $P < 0·001$ (McNemar test) there was a good level of agreement overall at 0·72. Regrouping of scores, with 0 denoting an occluded vessel and 1 a patent vessel (regardless of continuity with the pedal arch), and application of McNemar's test revealed a significant difference in favour of duplex imaging with regards to detection of patent vessels (χ^2 with Yates' correction = 67·14, 1 d.f., $P < 0{\cdot}001$).

Discussion

The ability to bypass occlusive disease by anastomosis on to distal tibial and pedal vessels has been achieved in vascular surgery and is particularly relevant in diabetic patients who often have isolated occlusion or stenosis of crural arteries[22–24]. The importance of the quality of the distal run-off in the context of these types of bypasses is supported by data from the literature[5,6]. Dardik *et al.*[5] reported that 15 of 17 grafts were patent at 6 months when the pedal arch was intact but all 11 grafts in limbs with an occluded arch failed. Accurate delineation of run-off with contrast arteriography in the face of critical ischaemia is impaired by the same high resistance which limits perfusion of blood to the periphery. The prevalence of missed run-off vessels is as high as 24 per cent in studies which compare preoperative MRA and conventional contrast imaging with verification of patency at surgery[25].

In comparative studies with arteriography, both pulse-generated run-off measurements and MRA have been validated against graft outcome[14,25]. The value of duplex for imaging the aortoiliac and femoropopliteal segments is well established and has the potential to replace diagnostic arteriography[26–28]. Until recently, there has been scant reference in the literature to duplex examination of tibial vessels[19,29,30]. Previous studies, however, compared duplex imaging with arteriography, assuming the latter to be the 'gold standard' and did not validate the findings with operative data. Since the assessment of distal run-off in patients with critical ischaemia is the very application for which preoperative arteriography may be suboptimal, it seems fallacious to use it as the comparative 'gold standard'. This study therefore validated duplex assessment of run-off against operative findings and graft outcome.

Duplex imaging fulfils many of the criteria that would be expected of an additional modality to supplement arteriography for the preoperative assessment of run-off in patients with critical ischaemia. In addition to anatomical imaging, it provides a functional evaluation based on flow signals and velocity criteria. It is technically simple to perform and takes 20 min to complete. It is well tolerated by patients and scanning can be performed through transparent, occlusive dressings despite infection and gangrene. There is a learning curve, and the peroneal artery is the most difficult vessel to image on account of its depth. Heavily calcified vessels can impede sonographic interrogation. The key to technical success is to commence scanning around the malleolar level where the tibial vessels are most superficial and to set the velocity ranges to detect the low flow velocities that might be anticipated in a patient with critical ischaemia.

The ultimate validation of the duplex findings would have been exposure of all three tibial arteries and direct arteriography of each vessel on the table. Clearly, this would have been impractical. Patients with critical ischaemia usually have just one, at most two, patent tibial vessels. During the study, no patient underwent on-table exploration in the hope of finding a patent vessel when preoperative investigations had found none. Therefore, no false-negative findings have been encountered with duplex imaging to date. In this study, the preoperative identification of a potentially suitable vessel, that is, patent and feeding an intact arch, was verified by the intraoperative finding of a soft, patent artery with brisk backbleeding and minimal downstream resistance on completion flow studies, together with a satisfactory arteriogram after reconstruction. This, together with the favourable cumulative patencies, provides ample validation of the duplex results and justifies the conclusions.

This study has demonstrated that colour duplex imaging is superior to arteriography for delineation of distal tibial and pedal run-off in critical ischaemia. Supported by the operative findings and follow-up, duplex reliability selected a suitable run-off vessel. Routine use of duplex for run-off assessment may obviate the need for blind surgical exploration and on-table arteriography before reconstruction.

As experience grows, duplex imaging of the entire lower limb arterial tree may supersede arteriography, allowing preoperative planning and management decisions to be made entirely on the basis of non-invasive assessment.

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Subfascial endoscopic perforator surgery is associated with significantly less morbidity and shorter hospital stay than open operation (Linton's procedure)

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Background Subfascial endoscopic perforator surgery (SEPS) is the minimally invasive alternative to the open (Linton's) procedure. This new technique may allow perforating vein interruption with fewer complications and a shorter postoperative hospital stay.

Methods This study was a case note review of 67 procedures: 30 SEPS and 37 Linton's.

Results There were no significant differences between the two groups in age, sex and indication for surgery. SEPS was associated with a significantly reduced postoperative stay in hospital (median 2 (range 1–49) days) compared with the Linton's procedure (median 9 (range 3–36) days) ($P<0{\cdot}01$). Nine patients who had Linton's procedure suffered a calf wound complication compared with none who had SEPS. The presence of an open ulcer at the time of surgery did not prolong the duration of stay in either group, nor did it increase the incidence of calf wound complications.

Conclusion In patients undergoing calf perforator interruption for chronic venous insufficiency, SEPS is associated with significantly less morbidity and a shorter hospital stay than Linton's procedure. SEPS can be performed safely at the same time as skin grafting and in the presence of an open ulcer without any increase in wound complications.

In 1938, Linton[1] described subfascial dissection and ligation of the perforating veins of the calf. Despite a number of modifications by Cockett (describing an extrafascial approach), Rob, Dodd and DePalma, the popularity of open perforator surgery waned because of the high incidence of complications and recurrent ulceration[2], together with an increasing use of sclerotherapy[3].

The advent of subfascial endoscopic perforator surgery (SEPS)[4] has rekindled the debate over the possible benefits of perforator interruption in the management of chronic venous insufficiency[5]. SEPS is a minimally invasive alternative to Linton's open procedure and may be associated with fewer complications and a shorter postoperative hospital stay. The aim of the present study was to examine the morbidity associated with SEPS and to compare it with that experienced in a historical series of patients undergoing Linton's procedure.

Patients and methods

The case notes of 61 patients who had interruption of calf perforating veins for lipodermatosclerosis and/or ulceration have been reviewed.

Thirty-one patients (22 men, nine women) of median age 55 (range 23–82) years underwent 37 Linton's procedures between January 1978 and July 1992. Thirty patients (13 men, 17 women) of median age 57·5 (range 37–83) years underwent SEPS (30 procedures) between September 1993 and July 1996.

Results

There were no significant differences with respect to age, sex or indication for surgery between the SEPS and Linton's patients. However, significantly more patients had the long saphenous vein stripped in the SEPS group (*Table 1*).

Patients who underwent SEPS had a shorter postoperative stay in hospital (median 2 (range 1–49) days) compared with those who had Linton's procedure (median 9 (range 3–36) days) ($P<0{\cdot}01$, Mann–Whitney U test) (*Fig. 1*). The patient in the SEPS group with a postoperative stay of 49 days had an open ulcer at the time of surgery and discharge was delayed because of failed skin grafting, not because of a complication of SEPS.

Nine patients in the Linton's group suffered a calf wound complication compared with none after SEPS. Calf wound complications (delayed wound healing (three), infection (four) and flap necrosis (two)) were the major

Table 1 Indication for perforator interruption and concomitant procedures

	Linton's procedure ($n=37$)	SEPS ($n=30$)
Indication for procedure		
Lipodermatosclerosis	5	5
Open ulceration	12	8
Healed ulceration	20	17
Concomitant procedure		
Perforator ligation alone	5	1
High saphenous ligation only	13	2*
High saphenous ligation and stripping	17	26*
Short saphenous ligation	5	8
Skin grafting	4	2

SEPS, subfascial endoscopic perforator surgery. $^*P<0{\cdot}01$ *versus* Linton's procedure (χ^2 test)

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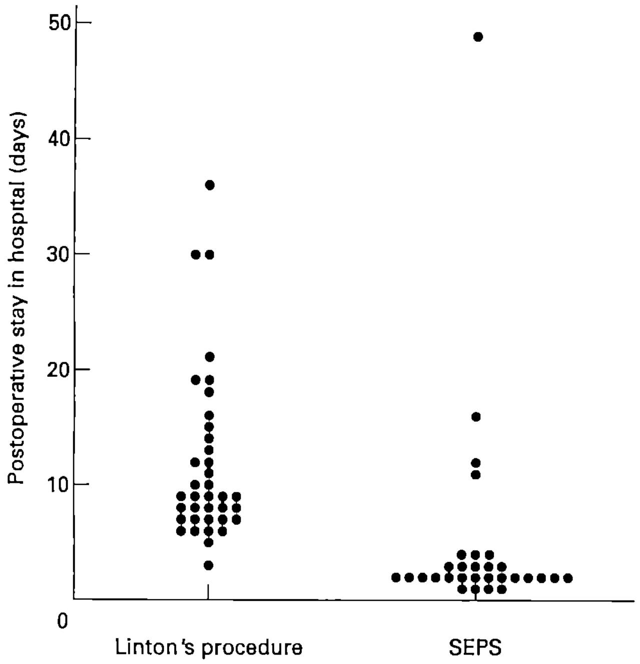

Fig. 1 Comparison of postoperative stay in hospital after Linton's procedure and subfascial endoscopic perforator surgery (SEPS)

Table 2 Postoperative complications

Complication	Linton's procedure ($n = 37$)	SEPS ($n = 30$)
None	21	22
Saphenous nerve injury	0	2
Deep vein thrombosis	1	1
Groin wound complications	3	3
Readmission	5	5
Calf wound complications	9	0*

SEPS, subfascial endoscopic perforator surgery. $*P < 0{\cdot}01$ *versus* Linton's procedure (χ^2 test)

cause of delayed discharge after Linton's operation. Other complications are shown in *Table 2*.

The presence of open ulceration at the time of surgery was not associated with a significantly prolonged postoperative stay in either group. For the SEPS group the median stay was 2 (range 1–49) *versus* 3 (range 1–15) days and in the Linton's group 10 (range 3–30) *versus* 9 (range 5–21) days for the open and healed ulcer groups respectively.

One patient in each group was readmitted for radiologically proven proximal deep venous thrombosis requiring anticoagulation.

Discussion

Although there is considerable controversy over whether interruption of calf perforating veins confers any additional benefit over standard saphenous surgery in patients with chronic venous insufficiency, SEPS is increasingly practised in both Europe and North America. The attraction of this minimally invasive technique is that calf perforating veins can be ligated and divided through a single 10-mm skin incision, placed in normal skin in the upper calf[2].

The patient discharge policy has changed on this unit in the past 20 years, as it has throughout the UK, with a shift towards shorter hospital stay. The present data regarding duration of stay in hospital must, therefore, be interpreted in this light. Similarly, it was with caution that tests of statistical significance were used to compare both the number of concomitant procedures and complication rates between two non-randomized groups. The greater number and severity of complications in the Linton's group remains, however, the most significant factor in the prolonged postoperative stay after this procedure

The advent of duplex ultrasonographic imaging and a better understanding of the causes and sites of varicose vein recurrence led to the increase in long saphenous vein stripping in the SEPS group. It is recognized that this may also improve the long-term outcome after SEPS.

The long-term results of the open Linton's operation performed for venous ulceration in this unit have been described previously[6]. The present study confirms the high rate of calf wound complications and, in keeping with many centres, Linton's procedure was abandoned when SEPS became available. SEPS is associated with little or no morbidity over and above what might reasonably be expected from concomitant saphenous vein surgery. SEPS is also associated with a significantly shorter hospital stay and may even be performed as a day-case procedure. These data show why in patients undergoing calf perforating vein interruption for chronic venous insufficiency, SEPS is now the procedure of choice.

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Prospective comparison of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the detection of bile duct stones

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Background Conventional ultrasonography is used widely in the investigation of gallstone disease but is limited in the detection of bile duct stones due to poor visualization of the distal bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) is currently the investigation of choice for suspected choledocholithiasis, but is not without morbidity. Endoscopic ultrasonography clearly visualizes the entire extrahepatic biliary tree and avoids the need for ERCP in many patients.

Methods Some 50 patients with suspected duct stones underwent endoscopic ultrasonography followed by ERCP. All cholangiograms were performed or interpreted by a second doctor blinded to the results of endoscopic ultrasonography.

Results Both tests were successful in 46 patients; both tests failed in two patients and ERCP alone failed in a further two. Duct stones were confirmed in 24 patients. Sensitivity (95 per cent confidence interval (c.i.)) of ERCP and endoscopic ultrasonography in identifying these stones was 79 (58–93) per cent and 88 (68–97) per cent respectively; specificity (95 per cent c.i.) was 92 (75–99) per cent and 96 (80–100) per cent.

Conclusion Endoscopic ultrasonography accurately identifies bile duct stones. It is recommended in all patients with a risk of duct stones but especially in those with a history of ERCP-induced pancreatitis, when other pathology is suspected, when ERCP has failed, when bile duct abnormalities are suspected during pregnancy and in patients with acute pancreatitis.

Endoscopic retrograde cholangiopancreatography (ERCP) is generally regarded as the 'gold standard' for the preoperative recognition of bile duct stones before laparoscopic cholecystectomy. Complications may occur, however, and a significant proportion of investigations are negative, even when applied to patients thought to be at high risk of harbouring bile duct calculi[1–4].

Although conventional ultrasonography is a useful first-line investigation for gallstone disease, it is limited in the investigation of bile duct stones, as visualization of the distal common bile duct (CBD) may be difficult and small stones in a non-dilated duct are easily missed[5,6].

Endoscopic ultrasonography can clearly visualize the entire extrahepatic biliary tree[6] and may be associated with less procedure-related morbidity than ERCP[7]. Despite increasing recognition of its role in the assessment of oesophageal disease, endoscopic ultrasonography has yet to be properly evaluated in the investigation of biliary disease.

If endoscopic ultrasonography could be shown to be sensitive and specific in the detection of bile duct stones, ERCP and its associated morbidity would be avoided in patients without bile duct stones. A prospective study was undertaken to ascertain the accuracy of endoscopic ultrasonography compared with ERCP in the investigation of suspected bile duct stones in patients awaiting laparoscopic cholecystectomy.

Patients and methods

Fifty patients with proven symptomatic gallstone disease and potential bile duct stones were studied. The criteria for suspected duct stones were any of the following features: dilated (greater than 7 mm) bile duct on abdominal ultrasonography, clinical jaundice, gallstone pancreatitis or deranged liver function.

Endoscopic ultrasonography was performed using the Olympus GF-UM 20 radial scanning echoendoscope (Olympus Optical, Tokyo, Japan). Anaesthetic throat spray and intravenous midazolam sedation were used with the patient in the left lateral position. The scope was introduced under endoscopic vision into the second part of the duodenum and scanning commenced at a frequency of 7·5 MHz, adjacent to the ampulla of Vater which is seen as a hypoechoic and well demarcated nodule (*Fig. 1*). The

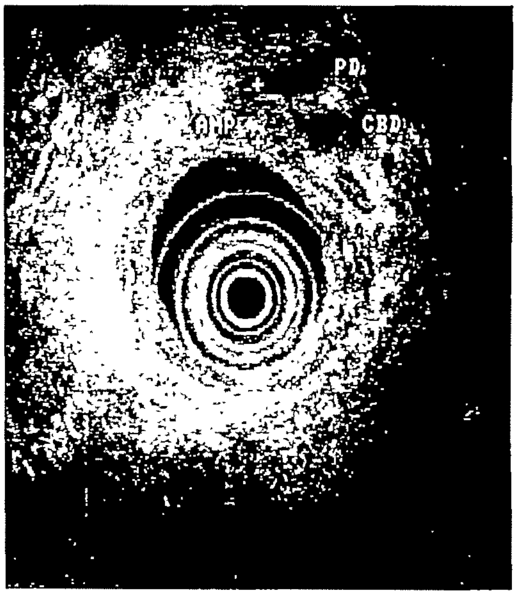

Fig. 1 Ampulla (AMP, between crosses) and lower end of common bile duct (CBD) and pancreatic duct (PD)

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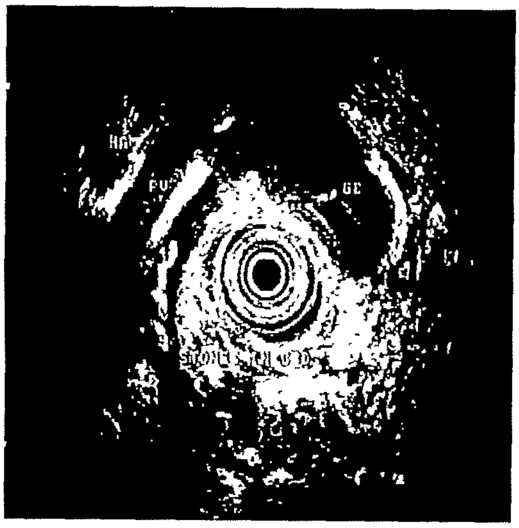

Fig. 2 Stones in common bile duct (CBD) seen as hyperechoic structures casting an acoustic shadow. HA, hepatic artery; PV, portal vein; GB, gallbladder

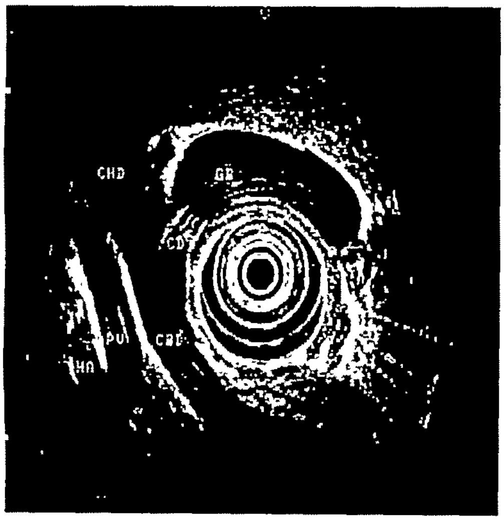

Fig. 3 Extrahepatic biliary tree and adjacent structures. CHD, common hepatic duct; CBD, common bile duct; CD, cystic duct; GB, gallbladder; HA, hepatic artery; PV, portal vein

CBD was identified and the presence or absence of stones noted. Stones were recognized by their hyperechoic image and the acoustic shadow commonly produced (*Fig. 2*). The common hepatic duct, right and left hepatic ducts, cystic duct and gallbladder were routinely sought and imaged (*Fig. 3*). The presence or absence of other pathology including lymphadenopathy was noted. Each procedure was videotaped for later reference.

ERCP was performed either immediately after endoscopic ultrasonography under the same sedation, or within the following 24 h. All cholangiograms were performed or interpreted by a second clinician blinded to the results of ultrasonography. Once the cholangiographic findings had been declared, however, the ultrasonographic results were revealed, allowing further intervention to be performed as necessary before withdrawal of the scope.

If either test suggested the presence of stones, endoscopic sphincterotomy was performed followed by attempted balloon extraction of the suspected stones and further completion cholangiography. Stones were retrieved during open cholecystectomy in one patient in whom ERCP failed.

The results of the two procedures were compared with the final diagnosis. In this way the two tests were compared individually with a 'gold standard' of retrieval of stones, either by endoscopic sphincterotomy or open operation. It is important to note, however, that when stones were not identified by ERCP or endoscopic ultrasonography, a presumptive diagnosis of no ductal stones was made. It was considered ethically unacceptable to perform sphincterotomy and balloon trawling of the bile duct to confirm the absence of stones. A final diagnosis (i.e. retrieval of stones or presumptive diagnosis of no stones) was reached in all 50 patients, and the diagnostic accuracies of endoscopic ultrasonography and ERCP are reported with respect to the total study population, including technical failures.

Results

Fifty patients (34 women) of median age 63 (range 17–83) years were suspected of having bile duct stones. Indications for endoscopic ultrasonography and ERCP are shown in *Tables 1* and *2*.

Both investigations were unsuccessful in one patient owing to intolerance of the procedures and in a second patient because of recurrent cardiac arrhythmias. At cholecystectomy one of these two patients was found to have choledocholithiasis. ERCP was not possible at the first attempt in a further two patients because of inability to cannulate the CBD. In one of these patients, endoscopic ultrasonography indicated the presence of stones; repeat ERCP was attempted successfully, and stones were retrieved by sphincterotomy. In the second patient, endoscopic ultrasonography indicated no stones; the patient was presumed to have no stones and subsequently underwent laparoscopic cholecystectomy with no subsequent symptoms suggestive of retained stones. Both investigations were performed successfully in the remaining 46 patients.

Although it is not possible to validate the presumption that when both tests were negative there were definitely no stones present, no patient categorized as such presented subsequently, either before or after laparoscopic cholecystectomy, with symptoms suggestive of retained stones (follow-up 6–13 months).

CBD stones were retrieved in 24 patients (23 after sphincterotomy and one at open cholecystectomy). ERCP identified stones in 19 and endoscopic ultrasonography in 21 of these patients, giving a sensitivity (95 per cent

Table 1 Indications for endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography

	No. of patients
Abnormal liver function test results	23
Jaundice	15
Dilated common bile duct	21
Pancreatitis	12

Table 2 Number of criteria fulfilled for suspicion of bile duct stones

No. of criteria	No. of patients
1	27
2	13
3	8
4	2

Table 3 Comparison between endoscopic retrograde cholangiopancreatography and presumptive final diagnosis in the detection of bile duct stones (based on 'intention to treat' results)

	Final (confirmed) diagnosis of CBD stones	Final (presumptive) diagnosis of no CBD stones
ERCP diagnosed CBD stones	19	2
ERCP diagnosed no CBD stones	5	24

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography

Table 4 Comparison between endoscopic ultrasonography and presumptive final diagnosis in the detection of bile duct stones (based on 'intention to treat' results)

	Final (confirmed) diagnosis of CBD stones	Final (presumptive) diagnosis of no CBD stones
Endoscopic ultrasonography diagnosed CBD stones	21	1
Endoscopic ultrasonography diagnosed no CBD stones	3	25

CBD, common bile duct

confidence interval (c.i.)) of 79 (58–93) per cent and 88 (68–97) per cent respectively. Stones were indicated by ERCP in two patients and by endoscopic ultrasonography in one patient in whom no stones were found, giving a specificity (95 per cent c.i.) of 92 (75–99) per cent and 96 (80–100) per cent respectively (*Tables 3* and *4*).

Two patients, one of whom had also undergone endoscopic sphincterotomy, developed pancreatitis (abdominal pain and amylase level greater than three times normal), which was presumed to be due to ERCP. No complications were observed that could reasonably be attributed to endoscopic ultrasonography.

Discussion

ERCP is a well established technique, used widely in the investigation of pancreatic and biliary disease. In the era of open cholecystectomy, suspected choledocholithiasis was usually assessed by intraoperative cholangiography[8], but since the advent of laparoscopic cholecystectomy the number of ERCPs performed has risen markedly as a means of identifying and removing bile duct stones before operation[8,9]. Intraoperative cholangiography is not performed routinely in many centres on the basis that laparoscopic exploration of the bile duct is perceived to be a difficult procedure[10]. The criteria for performing preoperative cholangiography to detect bile duct stones are set to minimize the risk of failing to identify the 3–35 per cent of patients with choledocholithiasis[11]. Despite attempts to refine these criteria[3,12,13], a high rate of negative ERCPs is often described (49–75 per cent)[2,4,10,14]. The procedure is not without complications: approximately 2 per cent of patients develop pancreatitis which may be life threatening[1,3,4,15].

With a significant likelihood of a negative result, a less invasive investigation that carries a lower risk of complications is needed. Endoscopic ultrasonography effectively visualizes the entire extrahepatic tree and accurately determines the presence or absence of bile duct stones[6,16]. Technical failure, due to inability to achieve biliary cannulation, is avoided. The lack of ductal cannulation makes endoscopic ultrasonography particularly attractive in the exclusion of stones in patients with acute pancreatitis, and as no radiological screening is required the technique is valuable in pregnant patients.

Endoscopic ultrasonography is able to visualize microlithiasis, which may be important in the development of acute pancreatitis[17]. The three false-negative results produced by ERCP were all in patients with small stones or microlithiasis in narrow ducts. In patients with symptomatic gallbladder stones who are due to undergo laparoscopic cholecystectomy, this may be unimportant as the source of microlithiasis will be removed, but such positive endoscopic ultrasonographic findings should prompt early surgery to avert the risk of pancreatitis. In addition, endoscopic ultrasonography is able to identify patients who present with acute pancreatitis due to microlithiasis thought to have a normal gallbladder on transcutaneous ultrasonography.

Endoscopic ultrasonographic findings may be difficult to interpret in patients with a previous biliary sphincterotomy when artefact from air within the biliary tree can mask stones. This was the cause of one of the two false-negative results in this study. With further experience this problem has been overcome by filling the duodenum and hence the bile duct with water during endoscopic ultrasonography.

The false-positive result with endoscopic ultrasonography was due to misinterpretation, early in the study, of soft tissue images at the ampulla, now readily recognizable as a normal variant. This can also be a problem with ERCP: one of the two false-positive results resulted from inability to distinguish between a filling defect due to a bulky ampulla and an impacted stone. With endoscopic ultrasonography the characteristic soft tissue echostructure was easily identifiable. The other false-positive result at ERCP was misinterpretation of Mirizzi's syndrome as a stone within the CBD. With endoscopic ultrasonography the stone was apparent within the gallbladder, surrounded by gallbladder wall and indenting the CBD.

Endoscopic ultrasonography is also able to identify other pathology, either within the gallbladder and biliary tree, or involving surrounding structures. Adenomatous polyps, for example, can be mistaken for gallstones on conventional ultrasonography or ERCP but are easily diagnosed on the high-resolution images obtained with endoscopic ultrasonography[15,16]. Early changes of chronic pancreatitis can be seen with endoscopic ultrasonography before they are apparent on ERCP[18–20]. In three patients in this study, changes associated with acute pancreatitis were clearly delineated by endoscopic ultrasonography (free fluid in the lesser sac, heterogeneity of the pancreatic tissue and localized fluid collections). Occasionally, an unexpected periampullary tumour may be the cause of symptoms. Endoscopic ultrasonography can identify the lesion and provide accurate staging in these cases[21,22].

Although endoscopic ultrasonography has the advantages of detecting microlithiasis and other pathology, it has the disadvantage that it cannot be combined with therapeutic manoeuvres. Endoscopic ultrasonography cannot therefore replace ERCP, implying that the consequence of carrying out routine endoscopic ultrasonography in patients who would otherwise undergo ERCP is that another test would be introduced into the diagnostic pathway.

These findings suggest, however, that routine use of endoscopic ultrasonography may be justified and cost effective. Should stones be identified by endoscopic ultrasonography, in the authors' experience it is simple to proceed immediately to sphincterotomy using a conventional duodenoscope. In this series endoscopic ultrasonography removed the need for ERCP in about half the cases, using widely accepted indications for ERCP. This conclusion is justified despite the relatively wide confidence intervals for the sensitivity and specificity of endoscopic ultrasonography because: (1) these values are as good as those for ERCP; (2) the consequences of missing a patient with CBD stones are identical to those following failed ERCP and the patient can be reinvestigated at a later date if symptoms persist; and (3) the lowest plausible estimate of the specificity of endoscopic ultrasonography (80 per cent) means that unnecessary ERCP can still be avoided in most patients without stones.

Endoscopic ultrasonography is therefore recommended in patients with a low but recognizable risk of bile duct stones, a history of ERCP-induced pancreatitis, when other pathology is suspected, when ERCP has failed, when bile duct abnormalities are suspected during pregnancy and in patients with acute pancreatitis.

Endoscopic ultrasonography can provide significantly more information on the bile duct, ampulla and surrounding structures than cholangiography. Like ERCP, it is a difficult procedure to perfect. Technically it is similar, but interpreting the images requires some practice. The results quoted represent the first 50 patients in whom the technique was attempted, suggesting that an experienced endoscopist, whether radiologist, surgeon or physician, would experience little difficulty in acquiring the necessary skills to use endoscopic ultrasonography for the identification of bile duct stones.

Alternative non-invasive approaches to biliary imaging such as magnetic resonance cholangiography will require prospective comparison against both ERCP and endoscopic ultrasonography in the future. Such comparisons should address both clinical issues and the cost-effectiveness of these approaches.

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Low mortality following resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units

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Background Recent studies have suggested that the mortality rate from pancreatic resection for cancer is high in the UK compared with that in published series. A survey of specialist units was conducted to determine whether the results differed from those in general units.

Methods The postoperative outcome following resection of pancreatic and periampullary tumours was analysed from specialist units in the UK and compared with that of other multi-institutional and large single institutional studies published recently (1900–1996).

Results A total of 1026 resections was reported from 21 units (33 surgeons). Postoperative complications necessitated reoperation in 57 patients (6 per cent) and there were 58 deaths (6 per cent) in hospital. Pylorus-preserving resections were performed in 102 (41 per cent) of 250 patients with ampullary adenocarcinoma undergoing a major right-sided resection and in 123 (32 per cent) of 381 patients with ductal adenocarcinoma of the head of the pancreas undergoing right-sided resection ($\chi^2 = 4{\cdot}01$, 1 d.f., $2P = 0{\cdot}04$). The mean number of resections for pancreatic ductal adenocarcinoma was 3·41 (range 1·0–7·1) per institution per year. Combining these data with those from the nine published series from specialist units, there was a lower mortality rate compared with the results of five published general surveys (median 4·9 per cent (95 per cent confidence interval (c.i.) 3·1–8·0 per cent) *versus* 9·8 (2·5–23·2 per cent), $2P < 0{\cdot}01$) and specialist units had a higher volume caseload (median 5·5 (95 per cent c.i. 4·2–8·1) *versus* 0·5 (–0·2–2·0) cases per institution per year, $2P < 0{\cdot}001$). Postoperative mortality was related to caseload both for the UK ($\chi^2 = 7{\cdot}17$, 1 d.f., $P < 0{\cdot}01$) and for all the data combined ($\chi^2 = 40{\cdot}4$, 1 d.f., $P < 0{\cdot}0001$).

Conclusion The results from specialist units in the UK compare favourably with those from specialist units outside the UK and are superior to those from non-specialist units. The mortality rate is generally lower in units with a higher caseload.

Pancreatic ductal adenocarcinoma has risen dramatically in incidence since the turn of the century and is now one of the commonest causes of death in Europe, North America and Australasia[1,2]. The incidence is continuing to rise in most parts of Europe, although in countries with a pre-existing high prevalence the increase appears to have peaked, at least for men[2,3]. Active treatment for pancreatic cancer has been viewed with considerable pessimism in the past because the postoperative mortality rate has been excessive[4,5]. A survey from the West Midlands Region of the UK revealed a resection rate of only 2·6 per cent and a 30-day postresection mortality rate of 28 per cent in the most recent 10-year period of the study (1977–1987)[1]. Thus it is not surprising that many clinicians, both gastroenterologists and general surgeons, view the prospect of resection with trepidation.

Nevertheless, the tide of worldwide opinion is slowly beginning to turn[6]. National data indicate a resection rate of 7 per cent[7], although institutional[8–13] and multi-centre[14,15] studies point to resection rates of 9–58 per cent, and the postoperative mortality rate has fallen from 20–30 per cent[16] to less than 10 per cent in many specialized units[8,9,11–13,17–19].

Only the West Midlands study has provided recent data on the outcome of surgery for pancreatic cancer in the UK, but these findings relate essentially to the experience of general surgeons[3]. Experience in other fields indicates that the best results are probably achieved by specialists, as recently shown by studies of outcome for colorectal[20] and breast[21] cancer. The present study therefore reports the results for surgical outcome of patients undergoing resection for pancreatic cancer and periampullary malignancy (which have a similar mode of presentation and treatment) by surgeons from specialist pancreatic units in the UK.

Patients and methods

During 1995 pro formas were sent by post to recognized pancreatic units, teaching hospitals and large district general hospitals in the UK and Ireland jointly by two of the authors (J.P.N. and R.C.G.R.), followed by several further mailings in 1995 and 1996 to encourage returns. Information was requested on at least 20 consecutive cases of pancreatic resection for neoplasia. The surgeons targeted included those belonging to the Pancreatic Society of Great Britain and Ireland and members of the UK Pancreatic Cancer Group (UKPACA) participating in UKPACA-1 and European Pancreatic Cancer Group (ESPAC-1) adjuvant trials. The aim was to collect data on postoperative outcome from at least 500 cases of pancreatic resection for malignancy from at least ten units.

The results were compared with those from other multi-institutional surveys and single institutional studies containing at least 50 resections published from 1990 to the present. Postoperative mortality was analysed in relation to volume caseload. To standardize the different time periods of data

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submitted to this study or published previously, the caseload was expressed as the mean number of cases of pancreatic cancer resected per institution per year.

Statistical analysis was by the χ^2 test (with Yates' correction) for categorical data and the Mann–Whitney U test for continuous data. Logistic regression[22] was used to model the relationship between postoperative mortality and volume caseload using software from BMDP Statistical (Los Angeles, California, USA). Significance was set at the 5 per cent level

Results

Data were analysed from 33 consultant surgeons working in 21 major centres (*Table 1*), and included one survey of 16 cases for 1 year only from one recognized unit. Data were also accepted from five other units, three with 14 cases each, one with 11 cases and one with ten cases; these were newly established but recognized units. Information was not included from 36 other institutions because there were too few cases to report in 35 and one well recognized unit failed to provide data. A total of 1026 resections was reported, comprising 421 resections (41 per cent) for pancreatic ductal adenocarcinoma, 134 (13 per cent) for endocrine and neuroendocrine tumours, 75 (7 per cent) for rare pancreatic neoplasms including cystic adenomas or carcinomas, 264 (26 per cent) for ampullary adenocarcinoma, 82 (8 per cent) for low bile duct cancer, 38 (4 per cent) for duodenal adenocarcinoma and 12 (1 per cent) periampullary cancers of indeterminate origin.

The types of operations performed and outcome are shown in *Table 2*; 57 patients (6 per cent) had reoperation for complications and there were 58 hospital deaths (6 per cent) following operation. Although information was requested on specific postoperative complications, this was largely incomplete from most units and was therefore not analysed. The relationship between postoperative

Table 1 Details of centres, numbers of surgeons and period covered

Centres ($n = 21$)	No. of surgeons ($n = 33$)	Period included
Birmingham – Queen Elizabeth and City Hospitals	4	1986–1995
Bristol – Royal Infirmary	1	1990–1994
Cardiff – University Hospital of Wales	1	1994–1995
Dundee – Ninewells Hospital	1	1994–1995
Edinburgh – Royal Infirmary	3	1991–1996
Glasgow – Royal Infirmary	2	1978–1994
Lancaster – Royal Infirmary	1	1990–1995
Leeds		
General Infirmary	1	1987–1994
St James' Hospital	1	1994–1995
Leicester – Royal Infirmary	4	1984–1994
Liverpool – Royal Liverpool University Hospital	1	1987–1994
London		
Middlesex Hospital	1	1976–1994
Royal Postgraduate Medical School	1	1979–1990
Royal Free Hospital	2	1988–1994
Manchester		
Hope Hospital	1	1992–1995
South Manchester University Hospital	1	1980–1995
Neath – General Hospital, Swansea	1	1993–1995
Newcastle-upon-Tyne – Freeman Hospital	1	1990–1994
Sheffield – Royal Hallamshire Hospital	3	1986–1994
Stoke-on-Trent – North Staffordshire Hospital	1	1992–1994
Southampton – General Hospital	1	1988–1994

Table 2 Results of surgery for all pancreatic and periampullary tumours

Unit	Total no. of cases	Resection					Mean no. of resections per year	Reoperation	In-hospital death
		Proximal	Total	Left	Enucleation	Local			
A	252	183	5	44	7	13	13·6	10	13
B	127	114	8	1	3	1	15·9	14	5
C	78	69	4	5	0	0	11·1	0	3
D	67	58	1	8	—	—	13·5	2	1
E	64	64	—	—	—	—	5·8	7	3
F	59	58	0	1	0	0	3·5	—	3
G	49	43	2	2	1	1	3·3	1	2
H	48	34	2	8	3	1	6·0	2	3
I	36	27	2	2	2	3	6·0	6	5
J	32	28	1	1	2	0	7·1	0	2
K	30	27	3	0	0	0	5·0	2	1
L	30	25	0	5	0	0	7·5	1	4
M	27	23	0	1	1	2	3·0	4	2
N	25	20	2	3	0	0	12·5	3	2
O	23	19	0	3	1	0	3·3	2	1
P	16	14	0	0	0	2	16·0	1	1
Q	14	9	1	3	1	0	5·6	1	0
R	14	14	0	0	0	0	0·3	1	3
S	14	14	0	0	0	0	2·8	0	3
T	11	11	0	0	0	0	5·5	0	0
U	10	9	0	0	1	0	3·3	0	1
Total	1026	863 (84)	31 (3)	87 (8)	22 (2)	23 (2)	150·6	57 (6)	58 (6)

Values in parentheses are percentages

mortality and caseload is described below. Outcome was specifically compared between resections for pancreatic ductal adenocarcinoma and ampullary adenocarcinoma, excluding all other types of neoplasm (*Tables 3* and *4*). There were no significant differences in the rates of reoperation or postoperative mortality following resection for these two specific types of malignancy. Significantly more patients with ampullary cancer than with pancreatic cancer underwent pylorus-preserving pancreatoduodenectomy (PPPD) compared with a conventional

Table 3 Results of surgery for pancreatic ductal adenocarcinoma

Unit	No. of cases	Resection			Mean no. of resections per year	Reoperation	Death	Median (range) hospital stay (days)
		Proximal	Total	Left				
A	66 of 252	57	3	6	3·7	3	4	18 (10–63)
B	57 of 127	56	1	0	7·1	6	1	14 (8–42)
C	42 of 78	38	4	0	6·0	1	1	17 (10–58)
D	27 of 67	22	1	4	5·4	1	0	12 (5–30)
E	27 of 64	27	—	—	5·8	—	0	17·7‡ (8–70)§
F	25 of 59	24	0	1	1·5	—	2	—
G	36 of 49	32	2	2	2·4	1	2	16 (11–39)
H	16 of 48	11	1	4	1·8	0	0	12 (8–29)
I	20 of 36	19	1	0	2·9	4	3	—
J	15 of 32	14	1	0	3·3	2	2	11 (7–28)
K	10 of 30	8	2	0	1·7	2	1	36 (24–28)
L	4 of 30	4	0	0	1·0	0	1	32 (23–32)
M	14 of 27	13	0	1	1·7	1	1	—
N	11 of 25	10	1	0	5·5	1	0	12 (9–27)
O	9 of 23	6	3	0	1·3	1	0	20‡
P	7 of 16	7	0	0	7·0	1	1	10 (7–26)
Q	7 of 14	5	1	1	2·8	0	1	14 (10–30)
R	10 of 14	10	0	0	5·7	0	1	—
S	9 of 14	9	0	0	1·8	1	3	13 (10–15)
T	4 of 11	4	0	0	1·5	0	0	20 (14–26)
U	5 of 10	5	0	0	1·7	1	1	18‡ (14–26)
Total	421 (41)*	381 (90)	21 (5)	19 (5)	71·6	26 (6)†	25 (6)†	11–36 (5–70)

Values in parentheses are percentages of *all pancreatic and periampullary tumours and †pancreatic tumours resected; ‡mean value; §range for all benign ($n = 36$) and malignant ($n = 64$) cases

Table 4 Results of surgery for ampullary adenocarcinoma

Unit	No. of cases	Resection			Reoperation	Death	Median (range) hospital stay (days)
		Proximal	Total	Local			
A	75 of 252	68	0	7	3	5	18 (8–127)
B	42 of 127	40	2	0	4	0	13 (8–72)
C	15 of 78	15	0	0	0	0	—
D	13 of 67	13	0	0	0	0	13 (9–30)
E	11 of 64	11	—	—	—	2	17·7‡ (8–70)§
F	24 of 59	24	0	0	—	1	—
G	5 of 49	5	0	0	0	0	17 (13–27)
H	11 of 48	10	0	1	1	0	14 (10–45)
I	5 of 36	3	0	2	0	2	—
J	3 of 32	3	0	0	0	0	11 (7–21)
K	10 of 30	10	0	0	0	1	20 (10–35)
L	12 of 30	12	0	0	0	2	27 (16–35)
M	5 of 27	5	0	0	2	1	—
N	4 of 25	4	0	0	0	1	13 (12–16)
O	8 of 23	7	0	1	0	0	40†
P	3 of 16	3	0	0	0	0	—
Q	3 of 14	3	0	0	1	0	10 (9–14)
R	4 of 14	3	0	1	0	0	—
S	5 of 14	5	0	0	0	0	10 (10–15)
T	4 of 11	4	0	0	0	0	15 (14–18)
U	2 of 10	2	0	0	0	0	—
Total	264 (26)*	250 (95)	2 (1)	12 (5)	11 (4)†	15 (6)†	10–27 (7–127)

Values in parentheses are percentages of *all pancreatic and periampullary tumours and †pancreatic tumours resected; ‡mean value; §range for all benign ($n = 36$) and malignant ($n = 64$) cases

Kausch–Whipple resection (*Table 5*) ($\chi^2 = 4\cdot04$, 1 d.f., $2P = 0\cdot04$).

The results of published data from five multi-institutional surveys of general surgical units and from nine single institutional studies of specialist units with more than 50 cases of resection for pancreatic ductal adenocarcinoma published from 1990 are summarized in *Tables 6* and *7*. Compared with the results of general surgeons from the West Midlands[3], the results from this UK series of specialist units revealed a significantly lower postoperative mortality rate ($\chi^2 = 47\cdot6$, 1 d.f., $2P < 0\cdot0001$). When the present UK series was combined with the results from specialist units from other countries[8–13,17–19] (*Table 7*) and compared with the results from multi-institutional surveys[3,14,15,22,23] (*Table 6*), the specialist units had a lower median postoperative mortality rate (4·9 (95 per cent confidence interval (c.i.) 3·1–8·0) per cent *versus* 9·8 (95 per cent c.i. 2·5–23·2) per cent, $2P < 0\cdot01$). Moreover, the median caseload was significantly higher in specialist units (5·5 (95 per cent c.i. 4·2–8·1) *versus* 0·5 (−0·2–2·0) cases per institution per year, $2P < 0\cdot001$).

Table 5 Number of pylorus-preserving pancreatoduodenectomies *versus* the number of standard Kausch–Whipple pancreatoduodenectomy resections for pancreatic ductal adenocarcinoma of the head of the pancreas and ampullary adenocarcinoma

	Pancreatic ductal adenocarcinoma			Ampullary adenocarcinoma		
Unit	Total	PPPD	Kausch–Whipple resection	Total	PPPD	Kausch–Whipple resection
A	57	23	34	68	32	36
B	56	14	42	40	10	30
C	38	30	8	15	13	2
D	22	0	22	13	1	12
E	27	11	16	11	3	8
F	24	0	24	24	14	10
G	32	0	32	5	0	5
H	11	0	11	10	2	8
I	19	3	16	3	1	2
J	14	0	14	3	0	3
K	8	6	2	10	10	0
L	4	0	4	12	0	12
M	13	4	9	5	0	5
N	10	10	0	4	3	1
O	6	2	4	7	4	3
P	7	0	7	3	0	3
Q	5	0	5	3	0	3
R	10	6	4	3	2	1
S	9	9	0	5	5	0
T	4	0	4	4	0	4
U	5	5	0	2	2	0
Total	381	123 (32)	258 (68)	250	102 (41)	148 (59)

Values in parentheses are percentages. PPPD, pylorus-preserving pancreatoduodenectomy

Table 6 Hospital mortality following resection for ductal adenocarcinoma of the pancreas reported in multi-institutional surveys since 1990

Reference	Year	Population base	No. of institutions	Period	No. of resections	Mean no of resections per institution per year	Hospital death	Mortality rate (%)
Bakkevold and Kambestad[15]	1993	Norwegian Multicentre Study	38	1984–1987	84	0·22	9	10·7*
Edge *et al*[23]	1993	University Hospital Consortium, USA	26 (91)	1989–1990	128†	2·46	10	7·8
Baumel *et al.*[14]	1994	French Association of Surgeons	148‡	1982–1988	787	0·89	77	9·8§
Bramhall *et al.*[3]	1995	West Midlands Region, UK	28	1977–1987	145	0·52	40	27·6*
Wade *et al.*[24]	1995	Department of Veterans Affairs Hospitals, USA	98#	1987–1991	252	0·43	21	8·3*
Present series	1996	Pancreatic surgeons (UKPACA), UK	21 (33)	1976–1996	421	3·41	25	5·9

Values in parentheses are numbers of surgeons. UKPACA, UK Pancreatic Cancer Group. *30-day mortality; §mortality rate at 1 month; †Kausch–Whipple resections only; ‡3 per cent response from private institutions and 19 per cent response from academic units; #no data returned from a further 61 hospitals

Table 7 Hospital mortality following resection for ductal adenocarcinoma of the pancreas from single institutions with 50 or more cases published since 1990

Reference	Year	Institution	Period	No. of resections	Mean no. of resections per year	Hospital death	Mortality rate (%)
Trede *et al*[11]	1990	University of Mannheim, Germany	1972–1989	133	7·8	3	2·3
Gall *et al.*[8]	1991	University of Erlangen, Germany	1969–1987	138	7·7	9	6·5
Geer and Brennan[13]	1993	Memorial Sloan-Kettering Cancer Center, New York, USA	1983–1990	146	20·9	7	4·8
Hanyu *et al.*[9]	1993	Women's Medical College, Tokyo, Japan	1978–1990	167	13·9	5	3·0
Takahashi *et al.*[10]	1994	Keio University, Tokyo, Japan	1976–1992	137	8·6	19	13·9
Allema *et al.*[17]	1995	Amsterdam Medical Centre, Holland	1983–1992	67	7·4	5	7·5
Nitecki *et al.*[18]	1995	Mayo Clinic, Rochester, Minnesota, USA	1981–1991	174	17·4	5	2·9
Yeo *et al.*[19]	1995	Johns Hopkins, Baltimore, Maryland, USA	1970–1994	201	14·4	10	5·0
Beger *et al*[12]	1996	University of Ulm, Germany	1982–1995	193	14·8	7	3·6

Table 8 Summary of logistic regression analysis on sets of data from the present UK series, published multi-institutional series and published specialist units, using the caseload to model the mortality statistics

	Improvement χ^2 for using caseload			Goodness-of-fit χ^2				
	χ^2	d.f.	P	χ^2	d.f.	P	Logit slope	Constant
Present UK series	7·17	1	0·007	14·0	15	0·53	0·3(0·12)	1·68(0·43)
Multi-institutional series[3,14,15,23,24]	14·18	1	<0·001	29·6	4	<0·001	0·29(0·08)	1·82(0·12)
Specialist units[8–13,17–19]	5·38	1	0·02	18·6	7	0·009	0·07(0·03)	2·1(0·37)

Values in parentheses are standard errors

Logistic regression analysis

Logistic regression takes the form

$$\log\left(\frac{P}{1-P}\right)=a+bc$$

where P is the probability of outcome (postoperative mortality), a is a constant, b is the slope and c is a variable (caseload). Logit transformation provides the improvement χ^2 statistic, which describes the significance (if any) of using caseload to predict postoperative mortality, and the goodness-of-fit χ^2 statistic describes the fit of the model such that if the latter is not significant it indicates little variation remaining in the data once the model is fitted, thus demonstrating a tightly fitting model. The results of this method of analysis for the present UK data on resection of pancreatic ductal adenocarcinoma and the two sets of published data (*Tables 6* and *7*) are shown in *Table 8*. Each of the three sets of data showed a highly significant improvement χ^2 statistic, indicating that caseload was a good predictor of postoperative mortality with the least variation in data demonstrated by the present UK series. Combining all three sets of data again revealed a significant improvement χ^2 statistic ($\chi^2 = 40·4$, 1 d.f., $P < 0·0001$), confirming the relationship between mortality and caseload but with a highly significant goodness-of-fit χ^2 statistic ($\chi^2 = 78·3$, 30 d.f., $P < 0·001$), exposing the particularly wide variation in data when combining such data sets. There was no significant difference between the logit models of the UK series and those of the multi-institutional series[3,14,15,23,24] ($\chi^2 = 0·17$, 2 d.f., $P = 0·75$), but both were significantly different from the logit model of the published specialist units[8–13,17–19] ($\chi^2 = 6·71$, 2 d.f., $P = 0·04$ and $\chi^2 = 8·03$, 2 d.f., $P = 0·02$ respectively).

The improvement χ^2 statistic for resection for all pancreatic and periampullary tumours in this series (*Table 2*) was $\chi^2 = 3·72$, 1 d.f., $P = 0·05$ for the association of resection rate and postoperative mortality, and the goodness-of-fit χ^2 statistic was $\chi^2 = 17·04$, 16 d.f., $P = 0·38$.

Discussion

Compared with other recent multi-institutional surveys[3,14,15,23,24] of resection for pancreatic cancer, the results from the UKPACA specialist surgeons compared favourably in terms of postoperative mortality (*Table 6*). The postoperative mortality rate of 6 per cent following resection of pancreatic ductal adenocarcinoma contrasts quite sharply with the value of 27·6 per cent obtained from the West Midlands Regional Survey, which included resections undertaken by all general surgeons[3]. Unfortunately, there are no other studies comparable to the West Midlands survey[3] from either the UK or any other country as this comprehensively covered every patient with a diagnosis of pancreatic cancer. Nevertheless, there are five multi-institutional surveys that did not specifically seek data from recognized pancreatic units and which may be considered representative to a reasonable degree of the results from general surgical units. In 1993, Edge *et al.*[23] reported the results of an audit from 26 of 50 member institutes of the University Hospitals Consortium (UHC) in the USA which participated in a clinical information network in 1989 and 1990. Surgeons with a caseload of fewer than four resections for pancreatic and ampullary cancer per year had a significantly higher complication rate than those performing four or more resections, but there was no significant difference in mortality rate. Of 158 hospitals belonging to the Department of Veterans Affairs (DVA) Hospitals in the USA, which reported treating pancreatic cancer, 98 gave detailed returns for the period 1987–1991[24]. There was no significant relationship between the number of cases resected per hospital per year and the 30-day mortality rate. Neither the Norwegian multicentre study[15] nor the French Association of Surgeons study[14] analysed outcome in relation to volume caseload, and it is noteworthy that 3 per cent of replies in the latter study were from private institutions and 19 per cent were from academic units.

The conclusion of the authors of the UHC and DVA studies was that caseload did not influence postoperative mortality assessed by either surgeon[23] or institution[24], but in both series there was a disproportionately low number of patients relative to the large number of institutions and surgeons included, exposing the analysis to a type II statistical error. Similar data to those derived from the West Midlands Region have come from the New York State Department of Health Survey (1980–1986), which demonstrated a mortality rate of nearly 30 per cent for institutions and surgeons with a low caseload compared with a rate of less than 5 per cent in experienced units, but this has been published only in abstract form[25]. The present UK series demonstrated a clear relationship between caseload and postoperative mortality. The similarity of the logit models of the data from the UK specialist units and the multi-institutional series[3,14,15,23,24], despite the mortality rate being significantly lower in the present UK series, merely points to the generally higher caseload of the latter. The difference between the models described above and the logit model of data published from specialist units[8–13,17–19] could be explained by the fact that none of the specialist units had a resection rate of fewer than seven cases per institution per year. In interpreting the logit models it is important to appreciate that the logistic regression analysis took into account the absolute number of cases included from each institution of series[22] such that the models generated were not unduly influenced by the larger number of units or series with the relatively fewer cases that they each contributed to the analysis.

These overall data suggest that a caseload of five to seven resections per year for pancreatic ductal adenocarcinoma is associated with a postoperative mortality rate of around 5 per cent or less. To surgeons undertaking complex surgery in other fields this caseload may appear unduly low, except that this should be considered to be a proxy figure for all pancreatic resections. In the present series pancreatic resections for ductal adenocarcinoma comprised only 41 per cent of all pancreatic resections for malignancy and no mention has been made of the number of resections for benign disease (principally chronic pancreatitis) in such units.

PPPD can be performed not only for ampullary tumours but also for pancreatic cancer provided adequate resection margins can be obtained[19,26–28]. Although there are no mature randomized studies comparing PPPD with the classic Kausch–Whipple resection in relation to long-term survival, all studies[19,26–30] but one[31] testify to a comparable outcome between these operations. Moreover, the PPPD procedure may have significant physiological advantages over the Kausch–Whipple resection, resulting in an improvement in quality of life[27,30]. Thus, it was encouraging to find that 15 of the 21 units were employing PPPD. As might be anticipated, there was a significant difference in the use of this procedure between patients with ampullary and pancreatic cancer, but the frequency with which PPPD was used in the latter group was comparable to that reported by a number of well established units outside the UK[19,27,30]. Some units, however, have been reluctant to adopt PPPD for pancreatic ductal adenocarcinoma as a matter of policy, reflecting a hesitancy in accepting the present data[19,25–29] in the absence of one or more large randomized trials.

Although the resection rate for pancreatic cancer amongst surgeons in the UKPACA group is rising yearly (data not shown), the mean was disappointingly low. This may reflect case selection by the surgeons but is more likely to indicate insufficient referrals from gastroenterologists to surgeons in general and to specialist surgeons in particular. The Norwegian Registry[7] revealed a resection rate of 7 per cent at a national level compared with 2·6 per cent in the West Midlands Region[3] (population 5·5 million). In England and Wales alone (population 51 million) there were 6034 deaths in 1992[32], which would equate to 422 resections per year assuming a 7 per cent resection rate, or 157 resections per year assuming a 2·6 per cent resection rate. Given an incidence of pancreatic cancer of approximately 12 per 100 000 population per year[1,3,32] and a 7 per cent resection rate[7], a specialist unit would require a population base of 600 000–850 000 to achieve five to seven resections per year respectively. This would equate to 66–93 units in the UK, all of which would need to receive referrals for resection of pancreatic cancer exclusively (or 24–34 units if the resection rate was only 2·6 per cent). The case for such units is further strengthened by the long-term survival rates being reported from specialist units[16]. Although long-term survival data were not collected for this study, other large series[3,8–19,23,24] have shown that a 5-year survival rate in the region of 10–24 per cent can be expected following resection and there is also the prospect of adjuvant treatment significantly prolonging survival even further[33,34].

The results of this survey demonstrate that UK surgeons specializing in pancreatic surgery achieved results which in general were comparable to those from well established and well publicised units elsewhere in Europe, Japan and the USA. Moreover, the data argue strongly in favour of concentrating pancreatic surgery into specialized units and, equally important, should encourage a higher referral rate from medical gastroenterologists exclusively to such units.

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Role of preoperative localization in the management of primary hyperparathyroidism

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Background The advantages of preoperative localization in the management of primary hyperparathyroidism have not been clearly demonstrated. The aim of this study was to investigate prospectively the accuracy of three localization techniques in patients with this condition.

Methods Forty-nine consecutive patients with primary hyperparathyroidism underwent ultrasonography, magnetic resonance imaging (MRI) and technetium–thallium (Tc–Tl) subtraction scanning before surgery, during which an attempt was made to identify all parathyroid glands. A scan was regarded as correct if it identified an enlarged parathyroid gland on the correct side of the neck as subsequently demonstrated at surgery.

Results Ultrasonography had a sensitivity of 38 per cent (18 correct scans in 47 patients) with a positive predictive value of 78 per cent. The sensitivity of MRI was 72 per cent (34 of 47) with a predictive value of 92 per cent. Tc–Tl scanning was 60 per cent sensitive (28 of 47) with a predictive value of 85 per cent. Two patients with negative neck explorations were subsequently found to have mediastinal adenomas.

Conclusion Ultrasonography, MRI and Tc–Tl scanning have limited value as localization techniques and the relatively low sensitivity of these investigations means they are of no value before first-time surgery.

The availability of routine serum calcium and intact parathyroid hormone determinations and an increasing awareness of the morbidity of chronic hypercalcaemia are factors that have led to an increasingly frequent diagnosis of primary hyperparathyroidism[1]. Surgery is successful in over 90 per cent of patients in specialist centres[2,3], offers a complete cure and has been advocated even for asymptomatic disease[4–6]. The reasons underlying failure of initial surgery to cure the disease may be surgeon, patient or pathologist dependent. Several studies have shown that abnormal parathyroid glands are often found at reoperation to lie in normal anatomical sites[7–9], suggesting that surgical experience plays an important part in the success of the initial operation[10]. Surgical 'failure' may also be due to the overlooked presence of more than one abnormal gland, an abnormal number of glands or glands in abnormal anatomical sites[11,12].

In an attempt to increase the chances of success at initial surgery, or to guide unilateral exploration, a variety of preoperative and intraoperative localization methods has been used; the earliest involved the preoperative injection of toluidine or methylene blue, with limited success[13]. Since then, several invasive and non-invasive techniques have been investigated[14]. The most widely employed techniques in current practice are ultrasonography, isotope subtraction scanning using a combination of technetium-99m and thallium-201 (Tc–Tl), computed tomography and magnetic resonance imaging (MRI). Recently a new imaging technique employing technetium-99m-sestamibi has been described which seems to show greater sensitivity than other methods[15]. Non-invasive preoperative scans probably have a role in the investigation of patients with previously failed surgery but their routine use before initial surgery remains controversial[16]. Many believe that the high success rate of primary surgery in experienced hands is not improved by preoperative imaging[17–20].

Preliminary results with MRI looked promising[21]. The aims of this study were to examine whether MRI is any better than ultrasonography or Tc–Tl scanning in the investigation of patients with primary hyperparathyroidism before initial exploration.

Patients and methods

A consecutive series of 38 women and 11 men with a mean(s.d.) age at operation of 57·0(14·4) (range 22–80) years was studied. All patients had clinical and biochemical evidence of primary hyperparathyroidism (*Table 1*). Median serum calcium concentration was 3·10 (range 2·64–4·60) mmol/l, median serum parathyroid hormone level was 16·0 (range 4·5–150·0) pmol/l.

Investigations

All patients underwent ultrasonography using a 7·5-MHz linear array probe. Tc–Tl isotope subtraction scanning was performed after an initial intravenous injection of 74 MBq of thallium-201 followed by an injection of 70 MBq of technetium-99m in the

Table 1 Presenting symptoms of 49 patients with primary hyperparathyroidism

Symptom	No. of patients
Polyuria or polydipsia	19
Weakness or lethargy	18
Bone pain	17
Renal calculus	14
Hypertension	11
Abdominal pain	7
Psychiatric disturbance	5
Pancreatitis	1
Asymptomatic or incidental finding	3

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form of pertechnetate. T1-weighted and short tau inversion recovery (STIR) images were obtained by MRI in the transverse plane using a slice thickness of 5 mm. The scans were interpreted by a single radiologist (J.K.) who reported the presence, number and anatomical site of abnormal parathyroid glands.

Surgery

Each patient underwent neck exploration by a single surgeon and both sides of the neck were explored with an intent to see all four parathyroid glands. Any gland that appeared abnormal was excised and sent for frozen-section histological examination. Serum calcium concentration was measured in each patient 24 h after surgery.

Analysis of radiological and operative findings

A scan was regarded as correct if it identified an abnormal parathyroid gland on the correct side of the neck as verified by surgery and histology No distinction was made with regard to upper and lower parathyroids in this study. Parathyroid adenoma was differentiated from hyperplasia by the absence of lobulation with associated loss of interlobular connective tissue. A histological diagnosis of parathyroid carcinoma was made if well defined cellular atypia was accompanied by evidence of vascular or capsular invasion. The radiological and operative findings were used to calculate the sensitivity and positive predictive value of each of the scanning methods

Results

Forty-seven patients had a positive neck exploration. Two patients with negative neck explorations were later found to have mediastinal parathyroid adenomas. Both of these were overlooked at initial MRI, although one had a positive Tc–Tl scan for the mediastinum. Both were localized by repeat MRI and excised at subsequent operation. The 47 abnormal parathyroid glands removed consisted of 44 adenomas and three carcinomas based on the histological criteria outlined above. No patient was found to have parathyroid hyperplasia. At 24 h the serum calcium concentration of every patient with a positive neck exploration had fallen. The median postoperative calcium level was 2·42 (range 1·90–3·20) mmol/l.

The results of the preoperative localization investigations are shown in *Table 2.* Ultrasonography was the least accurate of the three imaging techniques, mainly because of the high false-negative rate (51 per cent of scans). MRI showed a relatively high predictive value, with only three false-positive scans, but the ten false-negative scans resulted in a low sensitivity.

Table 2 Results of three preoperative localization techniques in 47 patients with positive neck exploration

Scan type	No correct	False positive	False negative	Sensitivity (%)	Positive predictive value (%)
Ultrasonography	18	5	24	38	78
Magnetic resonance imaging	34	3	10	72	92
Technetium–thallium subtraction scan	28	5	14	60	85

Discussion

Surgery is an effective treatment for primary hyperparathyroidism[22] and initial operation is successful in 90–95 per cent of patients[17–19]. The success of surgery decreases with subsequent operations, with a higher morbidity rate and a lower chance of establishing normocalcaemia[8]. This led to the examination of various preoperative and intraoperative strategies aimed at increasing the chances of a successful primary operation.

Ultrasonography has been employed extensively for imaging parathyroid glands since it was first used in 1979[23]. It is the least expensive and most convenient test because it does not involve the administration of isotope, dye or contrast. The low sensitivity and high false-negative rate in this study are in accord with those in previous reports[24–27].

Radioisotope subtraction scanning using thallium-201 was first described in this setting by Ferlin *et al.*[28]. The sensitivity of 60 per cent found in the present study agrees with other published results which report sensitivities of 40–90 per cent[29–31].

MRI gave the best results, although a sensitivity of only 72 per cent would severely limit its use as a localizing technique in previously unexplored patients. Other studies of MRI have reported sensitivities ranging from 50 to 93 per cent[32,33]. The complexity of MRI means that its potential as a localizing tool has not yet been explored fully. The superior soft tissue contrast may be particularly important in patients having repeat operation and in those with intrathoracic glands[7,21,34]. This is highlighted by the two patients in the present study who had negative neck explorations and in whom mediastinal parathyroid adenomas were subsequently located by MRI.

The variability in detection rate, which is a feature of all localization techniques, has never been explained adequately and makes comparisons between techniques reported from different institutions difficult. This is illustrated by studies that compare Tc–Tl scanning with ultrasonography. Some report Tc–Tl to be superior[35], whereas others suggest ultrasonography is superior[36]. Other studies show both techniques to be sensitive and complementary[37], although another study has concluded that neither technique is satisfactory[38].

Recent studies have examined technetium-99m-sestamibi subtraction scans[15]. Sestamibi was first described as a myocardial perfusion agent but was found to localize in parathyroid adenomas by Coakley *et al.*[39] in 1989. Many studies have shown a high specificity for preoperative localization of abnormal parathyroid glands using iodine-123 or technetium-99m as the thyroid pharmaceutical agent, or using a dual-phase technique that relies on the different washout kinetics of sestamibi from thyroid and parathyroid tissue[40–42]. Sestamibi does, however, have some disadvantages. Like other isotope scans, the technique is subject to motion artefact and the patient is required to receive a dose of radiation[41]. There are also reports of false-positive scans arising from the uptake of sestamibi in thymic remnants and thyroid adenomas[43,44].

The relatively low sensitivity of most localization techniques and the high success rate of primary surgery have led many surgeons to abandon preoperative imaging in the management of primary hyperparathyroidism. The arguments for routine use of imaging techniques are based on the fact that 80 per cent of parathyroid adenomas are solitary and only one side of the neck needs to be explored if an adenoma can be located before surgery. This reduces the duration of operation, which is more cost-effective with less risk to the patient[45–48]. Others take the view that, as parathyroid hyperplasia occurs in 10–15 per cent of patients[41] and double adenomas may occur in 9 per cent[49], bilateral neck exploration is mandatory. In this case preoperative investigations merely add to the cost of the operation[9,50].

MRI is no better than ultrasonography or Tc–Tl scans. No localization is warranted before first-time exploration for hyperparathyroidism.

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Short note

Communicating the result of breast biopsy by telephone or in person

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The conduct of the consultation in which a diagnosis of cancer is given can affect long-term adjustment[1-3]. Current guidelines suggest that patients should receive abnormal results in person[4]. This study investigates the satisfaction of patients given their result by telephone shortly after biopsy, or told in person at a later date.

Methods

A self-administered postal questionnaire was sent to 202 women. All had impalpable breast lesions detected at mammographic screening before September 1994. All had been seen personally preceding biopsy and prepared for all possible outcomes, although none had a preoperative diagnosis.

Results

Some 171 questionnaires (85 per cent) were returned. Seventy-six patients (44 per cent) had been told their result by telephone. Sixty-six (92 per cent) of 72 patients treated by C.T. had been telephoned, compared with ten (10 per cent) of 99 treated by R.M.W. (χ^2 with Yates' correction $= 236{\cdot}04$, 1 d.f., $P < 0{\cdot}001$). Sixty-nine (40 per cent) of all patients lived more than 20 miles from Derriford Hospital.

Some 84 per cent of patients telephoned (64 of 76) heard within 7 days, compared with 41 per cent (39 of 95) of those told personally (χ^2 with Yates' correction $= 28{\cdot}95$, $P < 0{\cdot}001$).

Seventy-one (93 per cent) of 76 patients telephoned were satisfied with hearing quickly in this way, including 42 of 43 patients with benign disease and 29 of 33 with malignant disease (P not significant). Fifty-nine (62 per cent) of 95 patients told their results in person were satisfied, including 45 (66 per cent) of 68 patients with malignant disease and 14 of 27 with benign disease (P not significant).

Overall, 93 per cent of those telephoned expressed satisfaction with the way in which they heard their result compared with 62 per cent of those told in person (χ^2 with Yates' correction $= 12{\cdot}56$, $P < 0{\cdot}001$). This was significant for the patients with benign disease (χ^2 with Yates' correction $= 10{\cdot}88$, $P < 0{\cdot}001$), and also for those with malignant disease (χ^2 with Yates' corection $= 4{\cdot}29$, $P < 0{\cdot}05$) (*Table 1*).

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Table 1 Satisfaction with method of communication of results

	Telephoned			Told in person		
	Benign	Malignant	Total	Benign	Malignant	Total
Satisfied	42 (98)	29 (88)	71 (93)	14 (52)	45 (66)	59 (62)
Not satisfied	1 (2)	4 (12)	5 (7)	13 (48)	23 (34)	36 (38)
Total	43	33	76	27	68	95

Values in parentheses are percentages

Discussion

The wait after breast biopsy before the diagnosis is known to be stressful. Imparting diagnoses by telephone minimizes this wait. The patient can assimilate results in private and prepare questions for subsequent outpatient appointments. Patients with benign disease and satisfactory wounds need not be recalled[5]. Potential disadvantages in telephoning are that unexpected calls may be upsetting or inconvenient and there are opportunities for misinterpretation. For the surgeon, repeated calls can take time and non-verbal cues are not available.

Giving results in person provides an opportunity for discussion and questioning. Non-verbal cues can be noted and the consultation paced accordingly. However, the patient has to wait for an appointment. Many patients feel uncomfortable in hospital and they may have to travel home when distressed.

A high proportion of patients who were telephoned with their results appeared satisfied. This might be expected when histology was benign, but most patients with malignant disease also appeared satisfied. Careful preparation is necessary and a skilled communicator essential. The personal technique of the surgeon may have been an important factor. A controlled prospective study would be valuable in further evaluating these findings.

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High serum carcinoembryonic antigen concentration in patients with colorectal liver metastases is associated with poor cell-mediated immunity, which is predictive of survival

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Background Carcinoembryonic antigen (CEA) inhibits lymphocyte function and patients with cancer have lower cell-mediated immunity (CMI) than the normal population. To test this association an investigation was made of the relationship between CMI score, CEA level and survival.

Methods CEA level, CMI score and other variables were compared with the survival time of 109 patients with colorectal liver metastases using Cox regression analysis.

Results There was a significant association between CMI and CEA categories ($P = 0{\cdot}04$, χ^2 test). The odds of patients with normal CMI having a CEA level in the upper quartile observed for all patients were 22 per cent of those of patients with depressed CMI (odds ratio 0·22 (95 per cent confidence interval (c.i.) 0·03–0·90), mid-*P* corrected). The median survival time of patients with normal CMI scores was 943 days compared with 488 days for those with depressed CMI ($P = 0{\cdot}03$, log rank test; $P = 0{\cdot}04$, Peto). The mortality risk of patients with normal CMI at entry to the study was, in the first 2 years of treatment, 40 per cent of that of patients with depressed CMI (95 per cent c.i. for relative risk 0·20–0·82, Cox regression).

Conclusion In patients with colorectal hepatic metastases, CMI is predictive of survival and a raised serum CEA level is associated with depressed CMI.

The glycoprotein carcinoembryonic antigen (CEA) is an intercellular adhesion molecule produced to a variable extent by more than 90 per cent of colorectal primary cancers[1]. Serum CEA concentration is of prognostic significance in patients with primary colorectal cancer and is currently the most sensitive tumour marker for liver metastases[2]. A raised serum CEA level is associated with both increased metastatic potential and a poorer prognosis from known liver metastases[3,4]. A fall in serum CEA concentration is predictive for increased survival in patients with liver metastases treated by resection, cryotherapy or regional chemotherapy[5–7].

Serum CEA concentration is a measure of tumour volume as well as of the amount of CEA that a given volume of tumour produces. The index, created by dividing serum CEA concentration by a volume measurement of liver metastases from colonic cancer, is more prognostic of survival than either CEA level or tumour volume alone[8]. The study, while small, was in a carefully selected group of patients who had no disease outside the liver and in whom the liver tumour volume was measured very carefully. This suggested that CEA may mediate an effect, possibly involving the immune system, which affects survival.

CEA does not directly stimulate colorectal cancer cell proliferation, but may promote metastases by interfering with cell adhesion, as well as directly inhibiting lymphocyte function by inducing the release of an immunosuppressive factor[9]. There are already good data indicating that CEA has a marked, direct inhibitory effect on lymphocyte function and that the ability of cell lines to produce liver metastases is related directly to their CEA production[10,11]. The preoperative serum CEA concentration of patients affects the ability of their tumours to grow in nude mice[12]. Injection of CEA into mice significantly increased the metastatic potential of a poorly metastatic colorectal cancer cell line, although it did not affect an already overtly metastatic line or a non-metastatic cell line[13].

In this paper, the authors examine the relationship between serum CEA concentration and the delayed cell-mediated immunity (CMI) of patients with liver metastases from colorectal cancer who were entering a randomized controlled trial of ranitidine treatment. This report concerns data from tests performed before trial entry which therefore cannot have been influenced by subsequent treatment.

Patients and methods

A total of 116 patients were studied at entry to a trial of ranitidine therapy for the management of colorectal liver metastases. Paired measurements of serum CEA concentration and Multitest CMI (Pasteur Merieux, Lyons, France) score were not available for seven of the patients, who were excluded from analysis Of the 109 remaining patients, 70 were men; mean age was 63 years; mean(s.d.) time from resection of the primary tumour to treatment of liver disease was 416(497) days, mean(s.d.) survival from study entry was 580(327) days, mean(s.d.) CMI score was 6·3(9·8) and mean(s.d.) serum CEA level was 295(830) ng/ml. One patient did not have resection of the primary colorectal cancer. There were 62 who had proven extrahepatic disease at study entry. Of the remaining 47 patients three had gross pelvic disease, 21 had abdominal lymphadenopathy, 13 peritoneal or perinephric disease, two bony metastases, seven pulmonary metastases and one had a synchronous pulmonary and liver metastasis resection. As treatment for liver metastases, 16 patients underwent liver resection,

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16 had cryotherapy and hepatic regional chemoperfusion, 62 had hepatic regional chemoperfusion, 11 had intravenous chemotherapy and four had no treatment

All patients had proven colorectal hepatic metastatic disease and were grouped according to whether or not they received chemotherapy for liver metastases. Treatment was dependent on the extent of metastatic liver disease Chemotherapy included cryotherapy and regional chemoperfusion via a hepatic artery catheter, hepatic artery catheter chemoperfusion or systemic chemotherapy. Patients who did not receive chemotherapy underwent liver resection or no treatment. Patients had baseline serum CEA estimation (Abbott MMX/AXYSM, Abbot Park, Illinois, USA) performed at study enrolment and CMI was tested with the Multitest CMI before commencing any trial medication.

The CMI Multitest is an applicator loaded with seven different antigens plus a glycerin control which delivers a simultaneous intradermal dose of tetanus, diphtheria, streptococcus, tuberculin, *Candida*, *Trichophyton* and *Proteus* antigens. Each subsequent cutaneous induration reaction is measured in millimetres horizontally and vertically at 48 h, the diameter is averaged and the scores are added A positive test is assessed as being no less than 2 mm in diameter. A Multitest CMI score greater than 10 is regarded as normal[14] Tests were performed, measured and scored for delayed hypersensitivity by one observer

Statistical analysis

The CMI score at study entry was categorized as normal (greater than 10) or not, and CEA levels were categorized according to whether or not they were in the top quartile for all 109 subjects (141 ng/ml or more). The association of these categorical variables was tested with the χ^2 test and summarized using an odds ratio. Both were calculated exactly from the binomial distribution and the 95 per cent confidence interval (c.i.) of the odds ratio was estimated using the mid-*P* adjustment (StatXact; CYTEL Software, Cambridge, Massachusetts, USA). The associations of patient descriptors with CMI category were summarized using a logistic regression with the outcome CMI category. The survival times of patients with low or normal CMI were summarized by means of a Kaplan–Meier function and the survival curves were plotted[15]. Cox regression was used to estimate the strength of the association of CMI category with survival time[16]. Observations for subjects who were still alive or who were lost to follow-up were censored, so they contributed to the total survival time but not to the total number of deaths. Cox regression permits allowance to be made for the effect of confounding variables when summarizing censored data. All 38 censored observations were for patients who were alive as at 1 December 1996.

Ten potential confounders were tested in the Cox models: age, sex, differentiation of primary tumour, number of liver metastases, diameter of largest metastasis, presence of metastases outside the abdominal and pelvic cavities, whether or not 25 per cent or more of the liver was replaced by tumour, concurrent plasma albumin level, whether or not the patient had received a course of chemotherapy, and whether or not the patient had been randomized to ranitidine.

Variables included in the Cox regression models were tested for conformity to the proportional hazards assumption using the *P*(PH statistic[17,18] and the models were tested for colinearity and influential observations. Time-dependent covariates were constructed for use in the final model, which was developed by backwards elimination of non-confounders so as to retain the estimated regression coefficient of CMI category while increasing its precision[19]. Cox regression analysis was performed and survival curves were fitted from the final model using the Statistical Package for Interactive Data Analysis (SPIDA) (Statistical Laboratory, Macquarie University, Sydney, Australia)[18]. Interim analysis of the effect of ranitidine on survival showed no effect. Full analysis is in progress

Results

Tables 1 and *2* show the continuous and categorical variables included in the Cox regression models below for normal and raised CMI. There were no significant associations between patient descriptors and CMI category. However, there was a significant association between CMI and CEA categories ($P = 0{\cdot}04$, χ^2 test). The odds ratio of patients with normal CMI to those with depressed CMI for a CEA level in the upper quartile of the values for the whole patient group was 0·22 (95 per cent c.i. 0·03–0·90), mid-*P* corrected. The median survival time of patients with a normal CMI score was 943 days compared with 488 days for those with depressed CMI ($P = 0{\cdot}03$, log rank test; $P = 0{\cdot}04$, Peto).

Table 2 Comparison of potential prognostic factors in patients with normal and depressed cell-mediated immunity

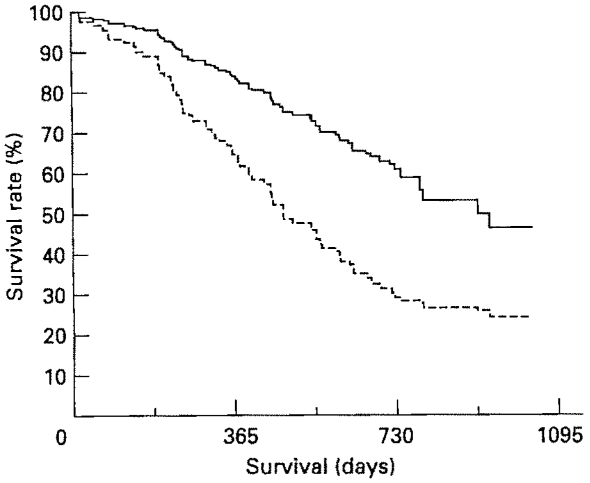
	Cell-mediated immunity score	
	≥10 (*n* = 23)	<10 (*n* = 86)
No. of censored patients	12 (52)	59 (69)
Categorical variable		
Male sex	20 (87)	50 (58)
Poorly differentiated primary tumour	5 (22)	10 (12)
More than six liver metastases	12 (52)	43 (50)
Largest metastasis >4 cm in diameter	9 (39)	40 (47)
Extrahepatic disease*	0 (0)	10 (12)
Hepatic replacement ≥25 per cent	2 (9)	15 (17)
Chemotherapy	22 (96)	67 (78)
Ranitidine	14 (61)	43 (50)

Values in parentheses are percentages. *Proven metastases outside abdomen or pelvis

Table 1 Age, albumin and carcinoembryonic antigen concentrations in patients with normal (greater than or equal to 10) or depressed (less than 10) cell-mediated immunity score

	Cell-mediated immunity score			
	≥10		<10	
Continuous variable	Mean(s.d.)	Median (range)	Mean(s.d.)	Median (range)
Age (years)	63·1(10·9)	65 8 (39–90)	62·8(11·5)	63·9 (37–88)
Albumin (g/l)	39·6(4·3)	41 (30–45)	36·9(6·0)	37 (19–50)
CEA (ng/ml)	47(76)	10·4 (1–325)	361(924)	43·8 (0–6220)
Cell-mediated immunity	22·9(8·5)	22 (11–45)	1·8(3·1)	0 (0–10)

CEA, carcinoembryonic antigen



No. at risk				
CMI > 10	23	20	14	5
CMI < 10	86	56	21	5

Fig. 1 Fitted curves displaying adjusted survival times of patients with normal (———) and depressed (– – – –) cell-mediated immunity (CMI) at time of entry to study

CMI score failed the test of conformity to the proportional hazards assumption, $P(\text{PH}) = 0{\cdot}05$, showing that the association of the CMI score with survival changed the longer the patients were in treatment. However, it was found that the relative risk was constant in the period 0–730 days and 731–1095 days and use of these time periods minimized the model's log likelihood. Patients with normal CMI were 60 per cent less likely to die in the first 2 years of treatment than those with depressed immunity at the time of study entry (relative risk 0 (95 c.i. 0·20–0·82); $P = 0{\cdot}01$, Cox regression). There was no statistically significant or clinically meaningful association between CMI category and survival after 2 years ($P = 0{\cdot}6$, Cox regression). Estimated survival curves for the two CMI groups (*Fig. 1*) were virtually identical to those plotted from the raw survival data using the Kaplan–Meier functions[15]. It can be estimated from the graphs that, although various patient and treatment factors were allowed for, patients with normal CMI at the time of study entry survived a median of 942 days compared with 468 days for those with depressed CMI.

Discussion

The hypothesis that the immune system has an important role in the defence against cancer is at present not well supported by clinical data. There are clearly many causes of immunosuppression in patients with cancer: tumour-specific factors, anaesthesia, surgery, chemotherapy and nutritional deficiencies. This is certainly well illustrated by the present data as, despite the strong relationship between serum CEA level and CMI, many patients with a CEA concentration below 1000 ng/ml were still anergic. The CMI Multitest skin test is a simple inexpensive method of assessing a patient's immunological status by evaluating delayed hypersensitivity to seven common antigens. Patients with cancer frequently have a low CMI skin test score. One study found that 98 per cent of healthy controls had a score greater than 5 and 90 per cent a score greater than 10 compared with 52 and 32 per cent respectively having scores above 5 and 10 in an untreated population of patients with cancer[20]. These results show for the first time that in patients with hepatic metastases from colorectal cancer a raised serum level of CEA is negatively associated with depressed delayed CMI and also that CMI is predictive of survival during the first 2 years after operation. The authors believe these data are likely to be due to the direct effects of CEA on lymphocyte function, which are well established in laboratory and animal experiments[9–13]. This knowledge may well provide a therapeutic target, although it is not yet evident whether there is a causal relationship producing a reduction in immune function. Prospective paired values of serum CEA concentration and CMI, together with survival data, may provide an answer to this question, as CEA levels fall in patients after successful treatment of liver metastases.

These results in patients with colorectal liver metastases confirm previous studies in patients with other types of cancer, which demonstrated that CMI can be prognostic of improved survival[21,22]. In this small descriptive study, unmeasured potential confounders were not controlled for, but the data show that high serum CEA concentration is associated with poor CMI and that CMI is predictive of survival.

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Liver resection in the elderly

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Background The operative mortality rate for hepatic resection in the elderly has been reported to be as high as 40 per cent for extended resection.
Methods An increasing need to justify use of limited healthcare resources prompted a prospective assessment of 133 consecutive hepatic resections performed in 30 months in patients over 65 years of age.
Results The overall mortality rate was 4 per cent. Mean(s.e.m.) hospital stay was 13(1) days, and admission to the intensive care unit was required for only eight patients. By univariate analysis, male sex ($P = 0{\cdot}003$), preoperative jaundice ($P = 0{\cdot}01$), abnormal preoperative electrocardiogram ($P = 0{\cdot}05$) and poor American Society of Anesthesiologists (ASA) physical status classification ($P = 0{\cdot}01$) were predictors of cardiopulmonary complications. In a multivariate analysis only male sex and ASA classification predicted complications ($P = 0{\cdot}05$). The 1-, 2- and 3-year survival rates for the entire group were 78, 66 and 50 per cent respectively. All survivors returned to good functional status (mean(s.e.m.) peak postoperative Karnofsky score 95(1)). When outcome was compared with that in 244 patients younger than 65 years of age who had liver resection during the same interval, the only difference was a longer mean hospital stay for the older patients: mean(s.d.) 13·4(0·5) *versus* 11·9(0·4) days for those aged less than 65 years ($P = 0{\cdot}02$).
Conclusion Major hepatic resection can be performed in patients over 65 years old with acceptable morbidity and mortality rates.

Primary tumours of the liver are among the most common solid tumours worldwide[1]. In addition, the liver is a common site for metastases[2]. More than 50 000 patients a year in the USA will have isolated metastatic disease to the liver from colorectal cancer alone; many are possible candidates for resection. Liver resection is not only effective but the only potentially curative therapy for primary liver cancer and for certain metastatic cancers[3]. In patients without associated liver parenchymal disease such as cirrhosis, resection of up to two-thirds of the liver can be performed with an operative mortality rate of less than 5 per cent[3,4].

The stress of liver resection may not be well tolerated in the elderly[5–9]. This is important because the high prevalence of liver cancers and the ageing of the world population have combined to increase the elderly population considered for liver resection[10]. Favourable results in young patients have encouraged the use of liver resection in all patients with liver cancer[3,11,12]. There is open debate whether major procedures such as heart surgery or dialysis should be performed in the elderly[13–15]. In this study the morbidity and mortality rates of potentially curative liver resection using current surgical and anaesthetic techniques were defined in the elderly. Some 133 consecutive liver resections in patients over 65 years of age were examined.

Patients and methods

All patients aged over 65 years admitted to this hospital for liver surgery between July 1991 and December 1993 were identified. Data for 133 patients were extracted from the database, hospital charts and office charts. Transfusion data were extracted from the computerized record system of the blood bank Clinical information on the patients was related to outcome. Routine follow-up for patients with malignant lesions was every 3 months for 2 years and every 6 months thereafter. Patients who lived at a distance from the hospital or with benign disease were followed by their local physician. In these cases, follow-up was by personal contact with the patient, patient's family or attending physician. The data from these 133 patients were compared with those from 244 patients aged less than 65 years who had liver resection during the same interval.

The extent of liver resection was defined by Goldsmith and Woodburne[16] Extended right hepatectomy refers to resection of Couinaud's segments[17] IV, V, VI, VII and VIII; an extended left hepatectomy refers to resection of segments II, III, IV, V and VIII; a right lobectomy is resection of segments V, VI, VII and VIII; and a left lobectomy is resection of segments II, III and IV. The American Society of Anesthesiologists (ASA) Physical Status Scores have been defined previously[18]. Functional status was assessed by the Karnofsky Performance Scale (KPS)[19] as follows: 100, normal; 90, normal activities with minor symptoms; 80, normal activities with effort; 70, cares for self but unable to carry out normal activities; 60, requires occasional care for most needs; 50, requires considerable assistance; 40, disabled; 30, severely disabled; 20, very sick, hospitalization necessary; 10, moribund; and 0, dead.

The χ^2 test or Fisher's exact test, where appropriate, was used for univariate comparisons. Multiple logistic regression was used to incorporate all of the explanatory variables in the same model[20]. Using the True Epistat statistical package (True Epistat, Richardson, Texas, USA), prognostic factors were determined for the hazard rate of complications. Differences were considered significant at the $P = 0{\cdot}05$ level. All deaths within 60 days of surgery were included in the surgical mortality rate.

Results

A total of 133 patients over 65 years of age had liver resection in the study interval. The median age of the

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patients was 70 (range 65–87) years. There were 79 men and 54 women. The majority of the liver resections were performed for metastases from colorectal cancer ($n = 83$, 62 per cent) or hepatocellular carcinoma ($n = 20$, 15 per cent) (*Table 1*). Forty-eight per cent of the 133 patients, and 24 of the 43 subjected to extended hepatectomy, had a history of cardiovascular disease. Of the 41 patients for whom preoperative cardiac ejection fraction was calculated either by echocardiography or radionuclide scan, in only two was it less than 45 per cent. Histopathologically proven cirrhosis was encountered in only eight patients (6 per cent), although 29 per cent had fatty infiltration, fibrosis or hepatic inflammation remote from the tumour.

Most patients required major liver resection: eighty-five procedures (64 per cent) involved resection of a lobe or more, and 43 (32 per cent) were extended hepatectomies (*Table 2*). Wedge or subsegmental resection was used in only 19 patients (14 per cent) and was influenced by the evidence that anatomical dissection and resection offers the greatest chance for safe and total removal of tumour The liver resections were performed using standard techniques including portal triad clamping[21]; no patient underwent complete vascular exclusion.

The gallbladder cancers and cholangiocarcinomas were solitary lesions. Of the 114 other malignancies, 30 were multiple. Median number of tumours in patients with multiple tumours was 3 (range 2–10). Median size of the malignant tumours was 5 (range 1·2–20) cm.

Mean(s.e.m.) operative blood loss was 1200(100) ml; median loss was 800 (range 50–8400) ml. The mean(s.d.) duration of hospital stay was 13(1) days, with a median of 11 (range 2–55) days. The practice during this study was to admit patients for arteriography and other imaging studies before surgery; the median postoperative stay for this group was 10 (range 1–53) days. The overall mortality rate (60-day or in hospital) was 4 per cent ($n = 5$), and for extended hepatectomy 7 per cent ($n = 3$). The overall complication rate was 47 per cent which included cardiopulmonary complications in 19 per cent (*Table 3*). Only eight patients (6 per cent) required admission to the

Table 1 Characteristics of elderly patients undergoing liver resection

	Extended hepatectomy ($n = 43$)	Lobectomy and minor resection ($n = 90$)	Overall ($n = 133$)
Mean(s.e.m.) age (years)	70(1)	72(1)	71(1)
Sex ratio (M:F)	27.16	52:38	79:54
Diagnosis			
HCC	10	10	20
Gallbladder cancer	3	2	5
Cholangiocarcinoma	2	5	7
Colonic metastasis	23	60	83
Other metastasis	4	7	11
Benign lesion	1	6	7
Associated medical conditions			
Cardiovascular	24	40	64
Previous MI	2	5	7
Previous CABG	5	3	8
Angina	3	10	13
Arrhythmia	1	10	11
Valvular disease	3	5	8
Pulmonary	7	17	24
Diabetes	4	10	14
Cirrhosis	2	6	8

HCC, hepatocellular carcinoma; MI, myocardial infarction; CABG, coronary artery bypass grafting

Table 2 Hepatic resections in patients over 65 years of age

	No. of patients ($n = 133$)
Left extended hepatectomy	8 (6)
Right extended hepatectomy	35 (26)
Left lobectomy	12 (9)
Right lobectomy	30 (23)
Bisegmentectomy	6 (5)
Left lateral segmentectomy	10 (8)
Segmentectomy	13 (10)
Atypical or wedge resection	19 (14)

Values in parentheses are percentages

Table 3 Complications of hepatic resection in the elderly

	Extended hepatectomy ($n = 43$)	Lobectomy or minor resection ($n = 90$)	Overall ($n = 133$)
Cardiopulmonary			
Angina	1	1	2
Arrhythmia	3	4	7
Myocardial infarction	0	2	2
Transient ischaemic attack	0	1	1
Congestive heart failure	0	1	1
Pneumothorax	1	0	1
Pulmonary embolism	0	1	1
Pneumonia	2	3	5
Infection			
Intra-abdominal abscess	2	2	4
Urinary tract infection	1	6	7
Wound infection	1	4	5
Phlebitis	0	1	1
HAI pump infection	1	1	2
Parotiditis	0	1	1
Pseudomembranous colitis	1	3	4
Gastrointestinal			
Liver insufficiency or failure	3	1	4
Intra-abdominal bleed	1	0	1
Mesenteric vein thrombosis	1	0	1
Prolonged ileus	1	1	2
Ascitic leak	1	0	1
Small bowel obstruction	1	1	2
Gastrointestinal bleed	0	1	1
Biloma	4	1	5
Miscellaneous			
Broken drain	0	1	1
Corneal abrasion	0	1	1
Dental loss	0	1	1
Fall	0	2	2
Deep vein thrombosis	2	0	2
Urinary retention	0	1	1

HAI, hepatic artery infusion

Table 4 Univariate analysis of predictors of complications

		All complications			Cardiopulmonary complications		
	n	No complications	Complications	*P*	No complications	Complications	*P*
Sex							
F	54	35	19	0·03	51	3	0·003
M	79	35	44		57	22	
Cardiac history							
No disease	69	37	32	0·9	60	9	0·1
Previous disease	64	33	31		48	16	
Jaundice							
None	128	70	58	0·02	107	21	0·01
Bilirubin level > 2·0 mg/dl	5	0	5		1	4	
ECG							
Normal	81	51	30	0·01	70	11	0·05
Abnormal	52	17	35		38	14	
ASA							
I	21	12	9	0·3	21	0	0·01
II	86	48	38		70	16	
III	26	10	16		17	9	
Size of resection							
Hepatectomy not extended	90	53	37	0·06	76	14	0·3
Extended hepatectomy	43	17	26		32	11	
Length of surgery (min)							
< 240	86	52	34	0·02	68	18	0·5
> 240	47	18	29		40	7	
Blood loss (ml)							
< 2000	116	64	52	0·2	96	20	0·4
> 2000	17	6	11		12	5	
Liver parenchyma							
Normal	95	50	45	0·8	78	17	0·9
Abnormal*	38	20	18		30	8	

ECG, electrocardiogram; ASA, American Society of Anesthesiologists *Fibrosis, steatosis, cirrhosis

intensive care unit; three of these had extended hepatectomy. There were five postoperative deaths. Two were related to technical factors. A 68-year-old jaundiced patient had a left lobectomy and bile duct excision for a hilar cholangiocarcinoma. A complex bile duct and portal vein reconstruction required prolonged liver ischaemia, and the patient died from progressive liver failure. A second patient had significant intraoperative haemorrhage during a right extended hepatectomy for metastatic colorectal cancer, and subsequently died from multiorgan failure the day after surgery. The remaining three deaths included a 72-year-old patient with chronic obstructive pulmonary disease who died as a result of aspiration pneumonia, and two patients (aged 69 and 85 years) who died from liver failure after extended right hepatectomy. With so few deaths, analysis for predictors of death was not appropriate.

Predictors of perioperative complications

Univariate analysis revealed that male sex, bilirubin level above 2·0 mg/dl, preoperative electrocardiographic abnormality and duration of operation greater than 240 min were predictors of complications (*Table 4*). History of cardiac disease, intraoperative blood loss or parenchymal liver abnormality was not predictive of complications. Considering cardiopulmonary complications alone, male sex, jaundice, electrocardiographic abnormality and ASA class predicted postoperative problems.

Sex, extent of resection, blood loss, ASA class and operating time were used as covariables in the multivariate analysis of predictors of complications after liver resection in these patients. Because jaundice was found in only five patients, this was not entered as a variable. By multiple logistic regression, male sex and ASA class were found to be significant predictors of complications after liver resection (*Table 5*).

Table 5 Multiple logistic regression analysis for risk of complications after liver resection in the elderly

Parameter	*P*	Coefficient (SE)	Relative risk
Sex	0·02	0·9	2·6
Extent of resection	0·06	0·8	2·3
ASA grade III	0·02	1·7	5·3

Covariables in this analysis were sex, extent of resection (extended hepatectomy, less than extended hepatectomy), blood loss greater than 2000 ml, American Society of Anesthesiologists (ASA) score and operating time. SE, standard error

When the mortality and complication data were analysed separately for age cohorts of 65–69, 70–74 and 75 years or more, no significant difference between these three groups was found.

Comparison with younger patients

During the 30 months of the study, 244 patients under 65 years of age underwent liver resection at the same institution. Of these 244 liver resections, 150 involved removal of a lobe of liver or more, and 76 were trisegmentectomies. The majority were performed for colorectal metastases (59 per cent). The relative number

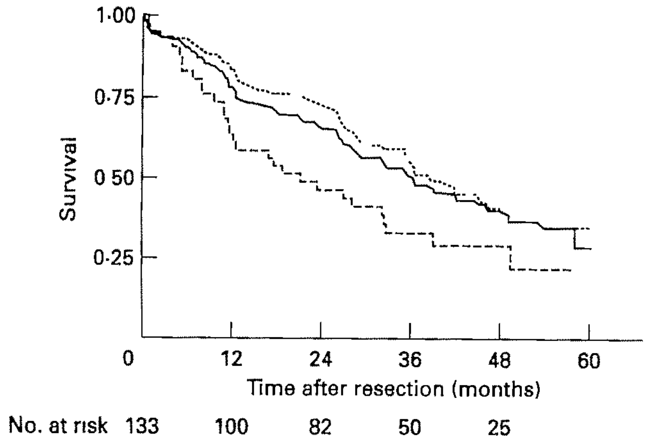

Fig. 1 Survival after major liver resection in the elderly. Kaplan–Meier curves are shown for all patients aged 65 years or more ($n = 133$; ———), patients who had resection of colorectal cancer metastases ($n = 83$; · · · · ·) and those who had resection of cancers not of colorectal origin ($n = 43$; – – – – –)

of major resections, as well as the relative numbers of resections performed for colorectal metastases, were similar for patients above or below the age of 65 years. The only outcome parameter that was significantly different was the duration of hospital stay. The younger patients had a shorter stay (mean(s.e.m.) 11·9(0·4) days) than those aged 65 years or more (13·4(0·5) days) ($P = 0{\cdot}02$).

Long-term outcome

Median follow-up for this group of 133 aged patients was 31 (range 1–62) months. Median time to death for the 74 patients who died was 17 months while median follow-up for the 59 survivors was 40 months. The 1-, 2- and 3-year survival rates for the entire group were 78, 66 and 50 per cent respectively (*Fig. 1*). For those who had liver resection for colorectal metastases the respective rates were 84, 73 and 55 per cent; the median survival for this group was 36 months. Of the 128 patients who survived the operation, 99 were followed longitudinally every 3 months at this institution and functional assessment was obtained by KPS. All patients returned to independent function (KPS 80 or more) with a mean(s.e.m.) peak postoperative KPS of 95(1). The median time to reach peak postoperative KPS was 3 months.

Discussion

Medical, social and financial forces dictate an increasing scrutiny of treatments for elderly patients. It is well documented that life expectancy for the world population is continuing to increase[10]. This, combined with escalating costs of sophisticated medical technology, has resulted in an increasing strain on healthcare budgets[13–15,22]. This study demonstrates that major liver resection can be performed in patients over 65 years of age with acceptable morbidity and mortality rates, and with hospital stays that rival those associated with surgical procedures considered routine[23,24].

Five previous studies specifically examined outcome of liver resection in the elderly[5–8,11]. Results were generally poor, with operative mortality rates as high as 19 per cent[8] to 40 per cent[6] even though most series included only a few major resections. Poor results in some series can be explained by a high proportion of patients with cirrhosis[6,8], but even in studies weighted towards patients without cirrhosis, an operative mortality rate as high as 30 per cent was noted for extended hepatic resection in the elderly[7]. Most previous reports were small; patients were therefore highly selected. In addition, these studies were retrospective and covered many years (median 13 (range 6–23) years). Recent improvements in operative and anaesthetic techniques could offer improved results. This report of 133 patients who had surgery in the past 2·5 years demonstrates that liver resection is safe in the elderly. The high proportion of major resections in this series (64 per cent) means that the elderly need not be denied extensive resection. The short hospital stay and the limited use of intensive care unit facilities indicate that spending of healthcare resources need not be exorbitant to achieve favourable outcome after liver resection in this group.

This experience comes from a tertiary referral cancer centre. Patients have had extensive screening by the referring physicians, and also locally. As a result of this selection process, no patient had an ASA score greater than III. Furthermore, only two of the 41 patients who had evaluation of cardiac function had an ejection fraction of less than 45 per cent. Nevertheless, the results are a testimony to the clinical selection of elderly patients who are likely to tolerate major liver resection. The present study is also the first large enough to allow statistical analysis of predictors of outcome. That ASA classification[25] and preoperative jaundice[26] are predictors of poor clinical outcome is not surprising.

Both major and minor liver resections can be performed safely in elderly patients. As with younger patients, jaundice, abnormal electrocardiogram or high ASA class are factors which should be used to select suitable patients. Chronological age alone should not be considered a contraindication to major liver resection.

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Hepatic microcirculation during human orthotopic liver transplantation

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Background Laser Doppler flowmetry (LDF) can measure blood flow in the hepatic microcirculation. Adequate graft perfusion is essential to the outcome of organ transplantation and has not previously been measured during operation in liver transplant recipients.

Methods LDF was carried out during operation in 22 human liver grafts after restoring portal vein and hepatic artery inflow. LDF readings were validated against liver blood flow with an electromagnetic flowmeter. Intraoperative haemodynamics and donor organ parameters known to influence graft function were correlated with LDF.

Results There was a significant correlation ($r = 0.96$, $P < 0.001$) between hepatic perfusion determined with LDF and total liver blood flow measured by electromagnetic flowmetry. The perfusion measurements were reproducible with a coefficient of variation of 4 per cent. Mean(s.d.) hepatic perfusion increased significantly from baseline following venous reperfusion (17(6) *versus* 114(37) flux units, $P < 0.001$). Arterial revascularization resulted in a significant increase in mean(s.d.) perfusion (32(4) per cent, $P = 0.02$). There was a significant negative correlation between cold ischaemia time and graft perfusion ($r = 0.48$, $P = 0.02$; $n = 22$).

Conclusion LDF provides a reliable non-invasive method of monitoring liver graft blood flow perfusion during transplantation.

Orthotopic liver transplantation (OLT) is now a routine procedure but initial poor function and primary non-function remain major complications resulting in significant morbidity, mortality and cost. Grafts with initial poor function have a high failure rate in the first 3 months after transplantation[1,2]. Primary non-function occurs in 5–10 per cent of grafts and is fatal unless urgent regrafting is performed[3,4]. There are many factors that influence the initial function of the transplanted liver but steatosis (fatty change) and prolonged preservation periods are the most clearly recognized causes[5,6]. Animal studies have demonstrated that the poor initial function of fatty livers following transplantation is associated with impairment of the microcirculation[5]. This suggests a possible role for assessment of the microcirculation in detecting and understanding the mechanism of primary non-function. Although ultrasonographic Doppler imaging[7–10] and electromagnetic flowmeters[11,12] have been used clinically to assess liver blood flow, they are cumbersome and do not measure liver parenchymal perfusion because of intrahepatic shunting and heterogeneity. Several methods have been used to assess liver perfusion in animal models, including estimation of hydrogen clearance[13], oxygen clearance[14], radioactive clearance[15] and laser Doppler flowmetry (LDF)[16–19].

LDF is a technique that allows microcirculatory tissue perfusion to be assessed without interference to the blood flow itself[18–20]. Only recently has it been applied to the measurement of perfusion in the hepatic microcirculation in animal experiments such as rat liver transplantation[21,22] and in clinically relevant large animal models[23,24]. Here, the use of LDF for measurement of the hepatic microcirculation during OLT in humans is reported. The effect on the hepatic microcirculation of the portal vein and hepatic artery blood flow has been studied, and the effect of the period of cold preservation of the graft on the hepatic microcirculation has been examined.

Patients and methods

Patient population

Twenty-two patients were studied while undergoing OLT. Profiles of the donors, recipients and grafts are summarized in *Table 1* Donor liver function tests were within the normal range. Preservation was with University of Wisconsin (UW) solution. All grafts were ABO compatible.

Laser Doppler flowmetry

The hepatic microcirculation was assessed using a commercially available laser Doppler flowmeter which is robust and fully portable (MBF3; Moor Instruments, Axminster, UK) A detailed description of the theory of the flowmeter operation and practical details of LDF measurement in the liver have been given elsewhere[19,23].

The Doppler signal varies linearly with the product of the total number of moving red blood cells in the measured volume of a few cubic millimetres multiplied by the mean velocity of these cells[19,23] The numerical product is termed perfusion units or blood cell flux[25].

The sensitivity of the laser Doppler flowmeter was checked before each study against a standard reference. The LDF probe was sterilized with gluteraldehyde (Cidex; Johnson and Johnson, Ascot, UK). To minimize any disturbance to blood flow, the optical fibre probe was mounted on a lightweight probe holder, and the actual probe was not in contact with the liver. This was applied to a fixed site on the left lobe of the liver as soon as the graft was inserted and the anastomoses of the inferior vena cava and portal vein were completed. A continuous reading was then obtained before revascularization and during reperfusion of the graft with portal and subsequently arterial blood LDF flux measurements were taken over a 2-min period at each of the following stages: (1) baseline reading before revascularization of

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Table 1 Profile of 22 donors, recipients and grafts

Donors	
Mean(s.d.) age (years)	44(12)
Mean(s.d.) body-weight (kg)	72(13)
Sex ratio (M:F)	12:10
Cause of death	
Subarachnoid haemorrhage	11
Diffuse head injury	1
Intracerebral haemorrhage	3
Head injury, road traffic accident	4
Meningitis	1
Respiratory insufficiency	1
Smoke inhalation, cardiac arrest	1
Recipients	
Mean(s.d.) age (years)	50(14)
Mean(s.d.) body-weight (kg)	67(10)
Sex ratio (M:F)	13:9
Primary disease	
Hepatitis C	9
Primary biliary cirrhosis	5
Retransplant (arterial thrombosis)	1
Chronic rejection	1
Graft ischaemia	1
Autoimmune CAH	1
Cryptogenic cirrhosis	2
Hepatocellular carcinoma	1
Hepatitis B	1
Grafts*	
Anhepatic time (h)†	1·02(0·23) (0·80–1·58)
Warm ischaemia time (h)‡	0·87(0·19) (0·62–1·37)
Cold ischaemia time (h)§	11·28(3·27) (2·20–14·80)

*Values are mean(s.d.) (range) time †from occlusion of the portal vein to restoration of portal vein inflow; ‡from insertion of the liver into the recipient to the restoration of portal vein inflow; and §from the start of cold perfusion in the donor to revascularization in the recipient. CAH, chronic active hepatitis

the graft; (2) 10, 20 and 30 min after perfusion of the graft with portal blood; and (3) 10, 20 and 30 min after perfusion of the graft with arterial blood. In one patient, serial readings on LDF were compared with liver blood flow at the same time periods. LDF readings during graded constriction of the portal vein were correlated with electromagnetic flowmeter (Nycotron Blood Flow Meter 376; Nycotron, Drammen, Norway) recordings of portal vein flow. This mimicked a previous animal study[21,24].

Reproducibility of the LDF readings was assessed by repeated readings from the same site and also by comparison between multiple sites. Portal vein blood flow was monitored during these readings with an electromagnetic flowmeter.

Data management and analysis

Results are expressed as mean(s.d.). Correlation between variables was made by least squares regression analysis. Differences in LDF signal between the stages of portal vein and hepatic artery revascularization were compared with analysis of variance with two factors without replication, and differences were considered significant when $P<0·05$. To estimate the reproducibility of the LDF, the mean(s.d.) coefficient of variability was calculated for each set of observations.

Results

Reproducibility

In one patient, the LDF probe was applied at four different sites on the liver with each application repeated eight times. The coefficient of variation of these data is presented in *Table 2*. The variation in each group of observations was very small and there were no significant differences in hepatic tissue perfusion between sites. Portal flow (2485(50) ml/min) showed minimal fluctuation during these measurements.

Table 2 Reproducibility of laser Doppler flowmetry recordings

Site on the liver	Mean(s.d.) flux units	Coefficient of variation (%)	No. of readings
Edge of left lobe	277(10)	4	8
Edge of right lobe	275(10)	4	8
Centre of left lobe	272(9)	3	8
Centre of right lobe	262(12)	4	8

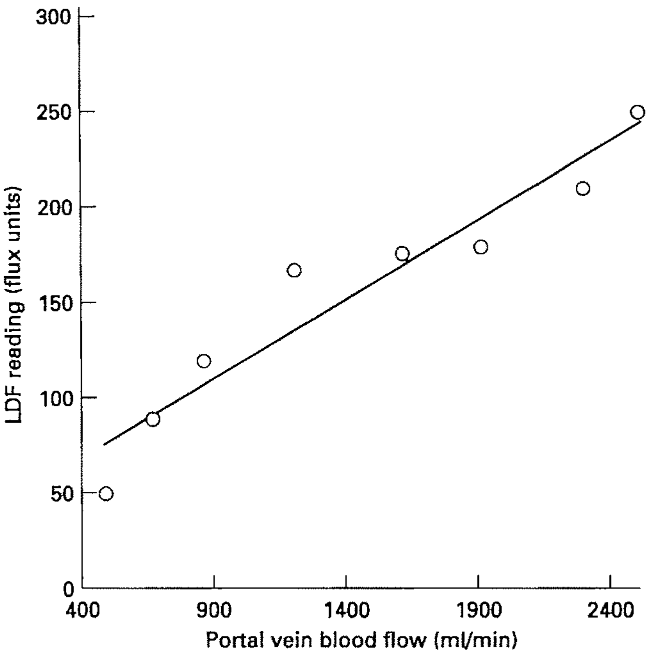

Fig. 1 Relationship of the laser Doppler flowmetry (LDF) reading from the surface of the left lobe of the liver to changes in portal vein inflow following graded constriction of the vein. $r=0·96$, $P<0·001$; $n=8$

Hepatic perfusion versus *graded portal vein constriction*

Fig. 1 demonstrates the highly significant correlation obtained between the LDF reading from the left lobe of the liver surface and the electromagnetic flowmeter reading from the portal vein ($r=0·96$, $P<0·001$). The instantaneous change in portal flow induced by constriction was reflected immediately and was maintained continuously on LDF.

Laser Doppler flowmetry readings from the liver surface

LDF readings before graft revascularization (baseline) and the rise at sequential time periods following portal and arterial reperfusion in 22 patients are shown in *Fig. 2*. As would be expected, there was a significant increase in perfusion following venous inflow (17(6) *versus* 114(37) flux units). The subsequent LDF measurement did not alter significantly with the time period following revascularization. The hepatic arterial revascularization resulted in a significant ($P = 0{\cdot}02$) increase of 32(41) per cent in perfusion. There was a slight decrease (16(27) per cent, $P = 0{\cdot}03$) in perfusion values over the 30 min following arterial revascularization. The baseline LDF reading is due to biological zero[26].

Fig 3 shows the relationship between cold ischaemia time and tissue perfusion at an early (10 min of portal vein inflow) and at a late (30 min of hepatic artery inflow) stage of graft revascularization. Prolonged cold ischaemia showed a negative correlation ($r = -0{\cdot}48$, $P = 0{\cdot}02$; $n = 22$) with graft perfusion (*Fig. 3a*) at the early phase of revascularization but not at the end of the operation (*Fig. 3b*).

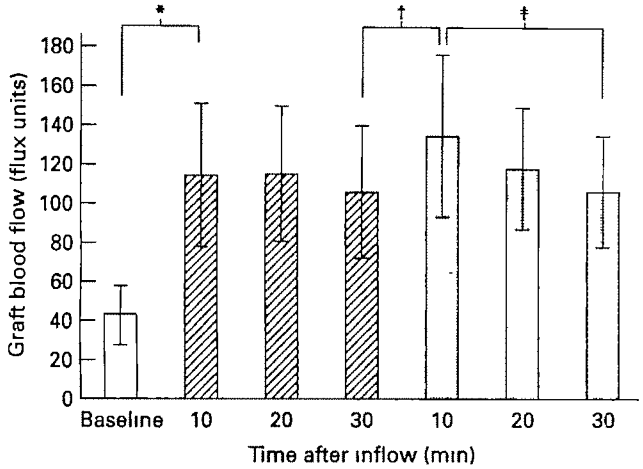

Fig. 2 Mean(s.d.) responses of the laser Doppler flowmetry reading from the surface of the left lobe of the graft liver to portal vein (▨) and hepatic artery (☐) inflow. $^*P < 0{\cdot}001$, $^†P = 0{\cdot}02$, $^‡P = 0{\cdot}03$ (analysis of variance)

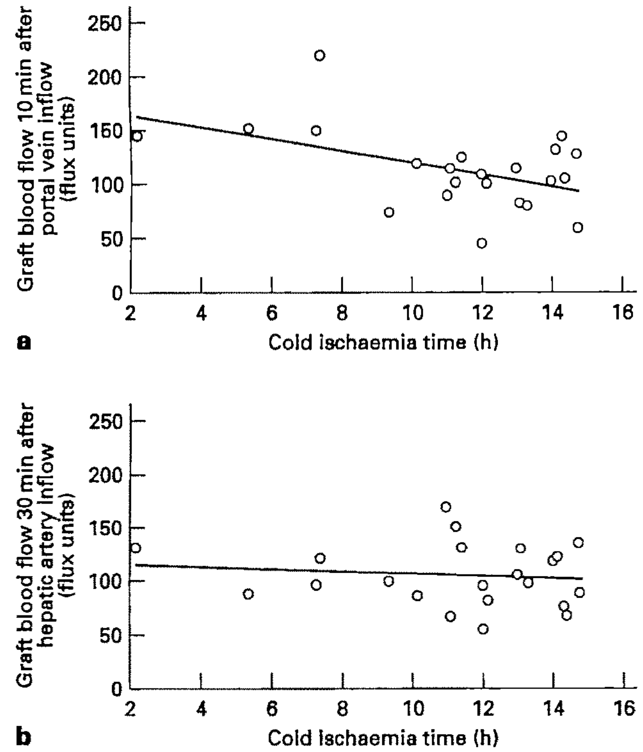

Fig. 3 Relationship between cold ischaemia time and graft microcirculation a 10 min after restoring portal vein inflow ($r = -0{\cdot}48$, $P = 0{\cdot}02$; $n = 22$) and b 30 min after restoring hepatic artery inflow ($r = -0{\cdot}11$, $P = 0{\cdot}61$; $n = 22$)

Donor and recipient factors and laser Doppler flowmetry

Donor age, donor:recipient weight ratio, warm ischaemia time and recipient anhepatic time had no significant effect on graft microcirculation as measured with the LDF.

Discussion

The authors have postulated that a technique to assess the hepatic microcirculation during OLT may help to understand the mechanism of liver graft damage and possibly predict graft function. Although many techniques have been used[19], only LDF allows continuous *in vivo* recording of the tissue blood flow, without directly affecting the microcirculation. This technique has not previously been assessed in patients during liver transplantation, although the authors have published a preliminary report of laser Doppler imaging[27].

The reproducibility of the LDF technique was assessed by measuring the coefficient of variation of multiple readings at the same site and between different sites. The value of 3–4 per cent is similar to that in a previous study of the laser Doppler flowmeter on the liver surface of the pig, in which a 6–8 per cent coefficient of variation was determined[23]. A study on human skin blood flow found a similar 4 per cent coefficient of variation[28]. It may have been expected that, in the complex situation of liver graft reperfusion, there would have been greater variation in values. This may be due partly to the repeated observations being performed on the liver graft after venous reperfusion but before the pulsatile flow associated with arterial revascularization. LDF measurements on the surface of the liver are a true reflection of graft perfusion, as the authors have demonstrated previously in a study comparing surface and intraparenchymal LDF probes[23]. Perfusion assessment with radiolabelled microspheres in animal models has also suggested that liver perfusion is relatively homogeneous[18,29,30].

In a single patient, portal vein inflow was gradually reduced while LDF was carried out repeatedly. A linear correlation was demonstrated between LDF findings and total liver blood flow ($r = 0{\cdot}96$). This is in agreement with previous animal studies showing a linear correlation between surface parenchymal LDF measurements and total liver blood flow determined by electromagnetic flowmeters[23,24]. LDF has also been studied in portally perfused rat livers, and a strong correlation ($r > 0{\cdot}9$ for perfusate haematocrits between 2·5 and 40 per cent) was found between LDF readings and total liver blood flow measured by timed collection of venous outflow[20]. LDF has also been compared with ^{85}Kr clearance for measuring the reduction in superficial liver blood flow with hepatic nerve stimulation. A mean(s.d.) LDF reduction of 12(10) per cent corresponded to a ^{85}Kr clearance fall of 14(10) per cent[20]. The effect of haemorrhage has also been evaluated in the rat, with a linear relationship being found between mean arterial pressure and LDF signal on the liver surface ($r > 0{\cdot}9$)[18].

Despite calibration of the LDF probe, there was a considerable variation in LDF readings between patients. This could be due to respiratory fluctuation, variation in portal vein and hepatic artery inflow, and intrahepatic shunting. This will need further investigation before LDF criteria for a well functioning graft can be established. However, the fact that all 22 patients initially had well functioning grafts shows that this range of LDF readings is indicative of successful vascular reperfusion and provides useful baseline data for further studies utilizing the laser Doppler flowmeter.

Protection of the liver against ischaemia and reperfusion injury remains one of the major problems of liver transplantation. Animal studies have suggested that oxygen-derived free radicals contribute to the cellular damage induced by ischaemia and reperfusion[31,32]. LDF studies of the hepatic microcirculation in the rat liver transplant model have shown that endothelial injury, resulting in incomplete return of blood flow to the hepatic microcirculation after reperfusion, occurs during liver ischaemia before widespread cellular damage[16,33]. In the rat liver transplant model, a correlation was demonstrated between reduced LDF findings and a prolonged cold preservation period of the graft, which reflected hepatic vascular damage during storage[16]. In human liver grafts the authors have shown a similar correlation. This relationship was demonstrated despite the cold preservation periods in this study of 2–15 h being well within the clinically useful preservation period for liver grafts in UW preservation solution[34]. This suggests that graft microvascular impairment is significant in routine clinical practice.

Repeat LDF measurements at the end of OLT, before abdominal closure, did not show any significant correlation with the preservation period. This may be due to the greater variation in LDF measurements as a result of pulsatile flow following arterialization or the variable effects of reperfusion on the microvasculature. Further studies will be required to clarify the relative importance of cold preservation and reperfusion to microvascular damage of the graft.

This study has demonstrated the potential of LDF in monitoring the liver microcirculation in patients undergoing liver transplantation. Ongoing studies are evaluating the role of LDF in assessing donor organs and in the early detection of complications after transplantation.

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Progress with cholecystectomy: improving results in England and Wales

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Background The Comparative Audit Service of the Royal College of Surgeons of England studied laparoscopic cholecystectomy in England and Wales during 1990–1991. The follow-on study undertaken during 1994 provides data to assess progress.

Methods Pro formas were sent to consultant surgeons, requesting data on open and laparoscopic cholecystectomies performed in their units during 1994 with data on mean stay, mortality, complications, and the use of peroperative cholangiography and bile duct exploration. The identity of the consultants was treated confidentially.

Results Data were provided by 110 surgeons on 4823 cholecystectomies (1019 open and 3804 laparoscopic) and outcome was compared with that of 3319 attempted laparoscopic and 8035 open cholecystectomies carried out during 1990–1991. The proportion of cases attempted laparoscopically rose from 27·2 per cent in 1990–1991 to 78·9 per cent in 1994, and conversion to open cholecystectomy rose from 5·3 to 6·7 per cent respectively. During 1994 peroperative cholangiography was undertaken in 22·9 per cent of laparoscopic and 44·6 per cent of open cases. Complication rates were similar in the two study periods, except the number of reported haemorrhagic complications was reduced by 40 per cent and bile duct injuries by fivefold (from 0·33 to 0·07 per cent).

Conclusion During 1994 the audit sampled approximately 10 per cent of all cholecystectomies performed in England and Wales. The results suggest progress in surgical techniques compared with findings in 1990–1991.

Laparoscopic cholecystectomy is still under intense scrutiny not only by surgeons and the medical community at large, but also by healthcare managers and by the print and electronic media. In the current environment, it behoves surgeons to keep records of the results and complications of their laparoscopic cholecystectomies, and to participate in local and national audit studies. The Comparative Audit Service of the Royal College of Surgeons of England had surveyed the results of 11 354 laparoscopic and open cholecystectomies performed during 1990–1991 when the laparoscopic procedure was being introduced in England and Wales. The results of that study[1] suggested that laparoscopic cholecystectomy was being carried out safely in a large number of centres in England and Wales. Complication rates were comparable to those reported in contemporary European and American national studies. A further study was organized by the same service to document the changes that had occurred since the previous survey.

Materials and methods

In February 1995, a booklet pro forma was circulated to consultant surgeons in England and Wales who may or may not have participated in the 1990–1991 survey, requesting data on the number of cholecystectomies (open, laparoscopic or converted) performed in their consultant units during the calendar year 1994. Data were also requested on mean stay, mortality, complications, and the incidence of peroperative cholangiography and bile duct exploration. The methodology was similar to that employed in the previous study[1] and complete confidentiality was assured to all participants. The identity of individual participating surgeons was not known to any of the authors, each set of data returned to the Royal College being identified only by a unique identifying number.

Complications were classified as major if they were life-threatening or significantly prolonged the postoperative stay of the patient. Otherwise, they were classified as minor. A request was made to group complications into the systems affected. For example, gastrointestinal complications would include ileus, bowel injury, diarrhoea, bowel obstruction, etc. Mortality and bile duct injury rates for laparoscopic cholecystectomy include these complications for converted cases, otherwise the data are for cases completed laparoscopically. Statistical analysis was by confidence interval analysis.

Results

Data were returned by 110 consultant surgeons, 54 of whom had participated in the 1990–1991 study. Of the total number of participating consultants, 26 were working in teaching hospitals and 84 in district hospitals. Information was received on the outcome of 4823 cholecystectomies in total, including 1019 open cholecystectomies reported by 98 consultants, 3549 laparoscopic cholecystectomies (100 consultants) and 255 cases converted from laparoscopic to open (65 consultants). The proportion of attempted laparoscopic cases went up from 29·2 per cent (3319 of 11 354 cases) in 1990–1991 to 78·9 per cent (3804 of 4823 cases) in 1994. Other differences are shown in *Table 1*.

Mean duration of postoperative stay, and the major and minor complication rates were virtually unchanged between 1990–1991 and 1994. The rate of conversion from laparoscopic to open cholecystectomy rose slightly from 5·3 per cent of cases in 1990–1991 to 6·7 per cent in 1994. Peroperative cholangiography was performed laparoscopically in 22·9 per cent of cases (538 of 2349

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Table 1 Laparoscopic cholecystectomies in 1990–1991 and 1994 reported to the Comparative Audit Service of the Royal College of Surgeons of England

	1990–1991	1994
Attempted laparoscopic cholecystectomy	3319	3804
Conversion to open cholecystectomy	175 (5·3)	255 (6·7)
Completed laparoscopic cholecystectomy	3144	3549
Mean stay (days)	2·7	2·6
No. of deaths	5 (0·2)	3 (0·1)
Major complications (%)	2·0	2·2
Minor complications (%)	5·9	6·1
Bile duct exploration*	20 of 3144 (0·6)	25 of 2395 (1·0)

Values in parentheses are percentages. *In cases completed laparoscopically

cases for which data were available) and in 44·6 per cent of open cholecystectomies (300 of 672 cases). A drop in the number of cases of intraoperative haemorrhage at laparoscopic cholecystectomy from 1·0 per cent in 1990–1991 to 0·6 per cent in 1994 was noted. Differences in systemic complications between the 1990–1991 and 1994 studies are shown in *Table 2*. Complications of open cholecystectomy from both studies are presented in *Tables 3* and *4*.

Discussion

The present study puts into perspective the rapid strides made in England and Wales in safely adopting the laparoscopic approach for cholecystectomy. Today, 79 per cent of cholecystectomies are undertaken laparoscopically in England and Wales. A survey of four European countries (Germany, Italy, UK and France) in 1993 showed that 378 000 cholecystectomies were performed, of which 52·6 per cent were carried out laparoscopically[2]. The rise in the conversion rate from laparoscopic to open surgery from 5·3 per cent in 1990–1991 to 6·7 per cent in 1994 may reflect the fact that more surgeons are prepared to adopt an 'all-comers' policy for laparoscopic cholecystectomy and may be willing to undertake the operation in those with acute cholecystitis and previous abdominal surgery, or alternatively that they have a more mature and sensible approach to conversion. The wide difference in the bile duct exploration rate (18·6 per cent for open cholecystectomy (190 of 1019 cases) *versus* 1·0 per cent for laparoscopic cholecystectomy (25 of 2395 cases)) suggests that most surgeons in England and Wales still prefer the open approach when dealing with known common bile duct stones.

Criticism[3] has been levelled at the authors' previous study[1] on the grounds that it was not a 'controlled trial' between laparoscopic and open cholecystectomy, which of course it was never intended to be. This study simply describes what happened to large numbers of patients receiving treatment for gallstones over a 3-year period. One reason why the two patient populations are not comparable is that one-fifth of open cholecystectomies are accompanied by bile duct exploration, whereas the corresponding value for the proportion of laparoscopic procedures is only 1 per cent. In the prelaparoscopic era, common bile duct exploration was carried out in about 9–11 per cent of open cholecystectomies[4,5], and now that most cases are operated on laparoscopically the incidence

Table 2 Comparison of the complications of laparoscopic cholecystectomy reported to the Comparative Audit Service in 1990–1991 and 1994

Complication	1990–1991* (*n* = 2728)	1994* (*n* = 2769)	Observed difference†
Wound infection	38 (1·4)	34 (1·2)	0·2 (−0·4–0·8)
Respiratory	20 (0·7)	26 (0·9)	−0·2 (−1·0–0·3)
Haemorrhage	28 (1·0)	16 (0·6)	0·4 (−0·0–0·9)
Cardiac	11 (0·4)	7 (0·3)	0·1 (−0·1–0·5)
Gastrointestinal	6 (0·2)	16 (0·6)	−0·4 (−0·7 to −0·0)§
Urological	26 (1·0)	18 (0·7)	0·3 (−0·2–0·8)
Metabolic	0 (0)	3 (0·1)	−0·1 (−0·2–0·0)
Central nervous system	5 (0·2)	3 (0·1)	0·1 (−0·1–0·3)
Retained stone	6 (0·2)	12 (0·4)	−0·2 (−0·5–0·1)
Bile duct injury	11 of 3319‡ (0·33)	2 of 2963‡ (0·07)	0·3 (0·1–0·6)§
Bile leak	35 (1·3)	40 (1·4)	−0·2 (−0·8–0·5)

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡Denominator includes converted cases. §$P < 0.05$ (confidence interval analysis)

Table 3 Complications and deaths following open cholecystectomy in 1990–1991 and 1994 reported to the Comparative Audit Service of the Royal College of Surgeons of England

	1990–1991* (*n* = 8035)	1994* (*n* = 1019)	Observed difference†
Major complications	203 of 6288‡ (3·2)	30 of 752‡ (4·0)	−0·8 (−2·2–0·7)
Minor complications	412 of 6288‡ (6·6)	74 of 752‡ (9·8)	−3·2 (−5·5 to −1·1)§
Deaths	55 (0·7)	5 (0·5)	0·3 (−0·3–0·7)

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡Denominator derived from all those submitting data on complications. §$P < 0.05$ (confidence interval analysis)

Table 4 Complications of open cholecystectomies in 1990–1991 and 1994 reported to the Comparative Audit Service of the Royal College of Surgeons of England

	1990–1991* ($n = 6288$)	1994* ($n = 752$)	Observed difference†
Wound infection	145 (2·3)	27 (3·6)	− 1·3 (− 2·6–0·1)
Respiratory	170 (2·7)	31 (4·1)	− 1·4 (− 2·9–0·1)
Haemorrhage	32 (0·5)	0 (0)	0·5 (0·3–0·7)‡
Cardiovascular	81 (1·3)	9 (1·2)	0·1 (− 0·7–0·9)
Gastrointestinal	55 (0·9)	11 (1·5)	− 0·6 (− 1·5–0·3)
Genitourinary and renal	134 (2·1)	14 (1·9)	0·3 (− 0·8–1·3)
Metabolic	20 (0·3)	2 (0·3)	0·0 (− 0·1–0·4)
Nervous system	20 (0·3)	2 (0·3)	0·0 (− 0·3–0·5)
Retained stones	32 (0·5)	10 (1·3)	− 0·8 (− 1·7–0·0)
Bile duct injury	4 (0·1)	0 (0)	0·1 (0·0–0·1)‡
Bile leak	65 (1·0)	4 (0·5)	0·5 (− 0·1–1·1)

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡$P < 0·05$ (confidence interval analysis)

of choledochotomy at open cholecystectomy has almost doubled.

Cardiorespiratory complications occurred in 5·3 per cent of open cholecystectomies in the present study and in 1·2 per cent of laparoscopic cholecystectomies. However, it would be a mistake to assume that the difference in complication rates between open and laparoscopic cholecystectomy was due simply to the increased bile duct exploration rate in open procedures. Complication rates remained similar even though the common bile duct exploration rate went up in the open cases. Also, the number of cases with exploration of the common bile duct is low, and complications in these are unlikely to affect the overall complication rate.

Another finding of this study was that the rate of peroperative cholangiography at open cholecystectomy dropped to 44·6 per cent in 1994 from a level of 90 per cent reported in an earlier survey[6]. Laparoscopic peroperative cholangiography was performed in less than one-quarter of cases in 1994.

Systemic complications remained more or less unchanged between the 1990–1991 and the 1994 studies for both laparoscopic and open cholecystectomy. Haemorrhagic complications at laparoscopic cholecystectomy reduced from 1·0 to 0·4 per cent between 1990–1991 and 1994. This may be due to increased laparoscopic expertise or to the realization that what appears to be heavy bleeding laparoscopically is often an insignificant small vessel bleeding on conversion to open surgery. Similarly, reported bile duct injuries have fallen from 0·33 to 0·07 per cent over the same period. Both these trends encourage the view that the standard of laparoscopic surgical practice may be improving. The bile leak rate remained unchanged and it is possible that a proportion of these cases may be due to minor bile duct injuries in both studies.

Overall, based on the data volunteered to this audit, the laparoscopic approach is being used for three of every four cholecystectomies carried out in England and Wales, with few haemorrhagic and bile duct injury problems. There has been a trend over the past 4 years to a slightly higher conversion rate (one in 15 cases) and a polarization such that patients known to require bile duct exploration are being selected for open cholecystectomy.

Given the limitations in the collection of data, the methodology of the Comparative Audit Service, and accepting that fewer cholecystectomies in total were audited than in 1990–1991, this audit of laparoscopic cholecystectomy represents a 10 per cent sample of all cholecystectomies undertaken in England and Wales during 1994. As such, this audit gives us the best guide available to surgical practice during 1994, and the results provide an indication of the mortality and morbidity that can be expected from cholecystectomy.

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Importance of microperineural invasion as a prognostic factor in ampullary carcinoma

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Background This was a study of the relation of clinicopathological factors to prognosis in 25 patients who had ampullary carcinoma resected.

Methods The 5-year survival rate was six of the 25 patients. The presence of microperineural invasion was sought and related to outcome.

Results Factors relating to prognosis included tumour gross appearance, diameter, pancreatic invasion and microperineural invasion. The 5-year survival rate of 14 patients with microperineural invasion was 3, significantly worse than the 7 in 11 without invasion ($P = 0{\cdot}002$, univariate analysis). By multivariate analysis, microperineural invasion was the most important prognostic factor ($P = 0{\cdot}02$). Type of tumour recurrence was similar to that in pancreatic carcinoma.

Conclusion Pancreaticoduodenectomy, rather than local resection, is the procedure of choice in patients with ampullary carcinoma.

Ampullary carcinoma is generally resectable and has a favourable prognosis[1–4] compared with other pancreatic tumours. A poor prognosis after resection has been related to tumour diameter, histological type, presence of lymph node metastases and pancreatic invasion[4–12]. In bile duct or pancreatic carcinoma, perineural invasion is an important prognostic factor[13–15]. The incidence of perineural invasion is lower in ampullary carcinoma and it has not previously been considered a prognostic factor. In the present study immunohistochemical staining was used to determine the importance of microperineural invasion compared with other clinicopathological factors as a prognostic factor in ampullary carcinoma.

Patients and methods

The subjects were 25 patients with ampullary carcinoma who had pancreaticoduodenectomy between August 1980 and June 1994. There were 14 men and 11 women of mean age 63 (range 45–80) years. The following were evaluated: tumour gross appearance, diameter, histological type, duodenal invasion, pancreatic invasion, lymph node metastasis, lymphatic vessel invasion, blood vessel invasion and microperineural invasion.

Evaluation of microperineural invasion

Nerve fibres were stained immunohistologically with antinerve fibre antibody (S-100). Several specimens were prepared from the centre of the primary lesion and microperineural invasion was recorded as positive if cancer cell infiltration to nerve fibres was detected at the leading edge

S-100 staining was carried out as follows: resected specimens, fixed in 10 per cent formalin, were embedded in paraffin. Sections, 4-μm thick, were stained using the ABC method (ABC Kit; Vector Laboratories, Burlingame, California, USA) Anti-S-100 antibody (DAKO, Copenhagen, Denmark), diluted 1:200, was used as the primary antibody and reacted for 30 min at 37°C. DAB (Wako Pure Chemical Industry, Tokyo, Japan) was used for colouration.

Microperineural invasion was positive when S-100 staining resulted in a clear appearance of nerve fibre bundles of diameter 50 μm or greater (*Fig 1*). Microperineural invasion was seen in 14 of the 25 patients, a higher incidence than that of perineural invasion (three of 25) seen with haematoxylin and eosin staining. All three perineural-positive patients were also positive for microperineural invasion.

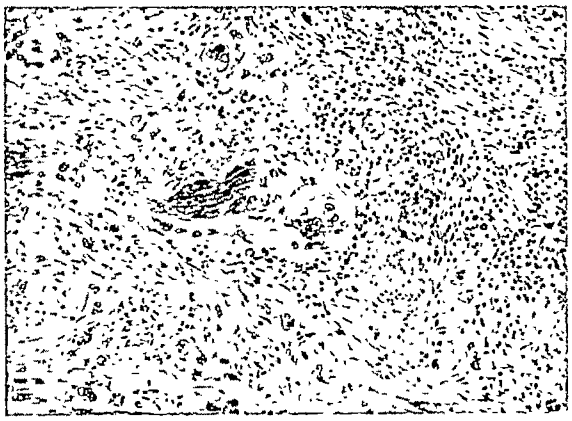

Fig. 1 Microperineural cancer invasion in the nerve fibres (S-100 staining; original magnification × 100)

It was confirmed by S-100 staining that there was no neural invasion in either the extrapancreatic nerve plexuses or the ablated surface of the posterior pancreas.

Survival rates were calculated with the Kaplan–Meier method[16]; statistical analysis was with the Mantel–Cox test. A Cox proportional hazards model[17] was used to test for independent predictors of survival. $P < 0{\cdot}05$ was considered statistically significant.

Results

In the 25 patients, both 3- and 5-year survival rates were 11 and six of the 25 patients (*Fig. 2*). The tumours were classified histologically by means of the Union Internacional Contra la Cancrum tumour node metastasis (TNM) system: stage I, seven patients; stage II, ten; stage III, seven; and stage IV, one patient. Factors significantly related to outcome on univariate analysis included tumour appearance and size, and pancreatic invasion. Patients

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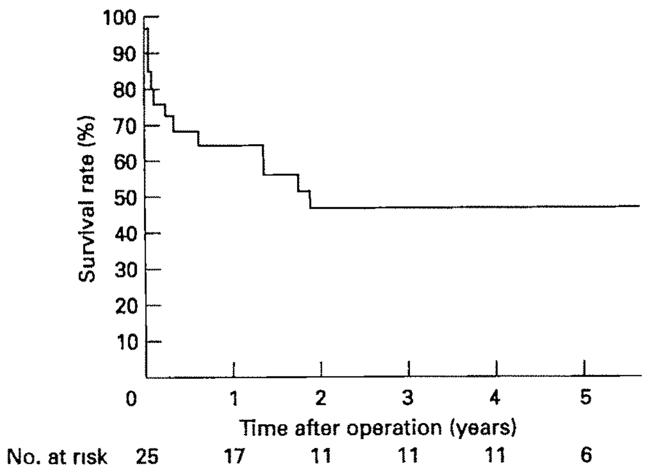

Fig. 2 Cumulative survival rate in 25 patients after pancreaticoduodenectomy for ampullary carcinoma (Kaplan–Meier method)

Table 1 Clinicopathological factors affecting survival in 25 patients after resection for ampullary carcinoma (univariate analysis)

Clinicopathological factor	No. surviving 5 years	*P*†
Gross appearance		
Protruding type	10 of 15	0·008
Ulcerating type	2 of 10	
Tumour size (cm)		
≤ 2	8 of 12	0·001
>2	2 of 13	
Histological type		
Papillary adenocarcinoma	7 of 12	0·06
Tubular adenocarcinoma	3 of 13	
Pathological factors		
Duodenal invasion		
No	6 of 8	0·03
Yes	5 of 17	
Pancreatic invasion		
No	10 of 17	0·003
Yes	1 of 8	
Lymph node metastasis		
No	8 of 16	0·06
Yes	2 of 9	
Lymph vessel invasion		
No	4 of 10	0·25
Yes	6 of 15	
Blood vessel invasion		
No	6 of 16	0·61
Yes	4 of 9	
Microperineural invasion*		
No	7 of 11	0·002
Yes	3 of 14	

*With S-100 staining; †Cox–Mantel test, statistically significant ($P<0{\cdot}01$)

with microperineural invasion ($n=14$) had a 5-year survival rate of three, significantly worse than the rate of seven in 11 patients without invasion ($P=0{\cdot}002$) (*Table 1*).

Using multivariate analysis, the following clinicopathological factors significantly affected outcome ($P<0{\cdot}01$): gross appearance, tumour diameter, pancreatic invasion and microperineural invasion (Cox proportional hazards model). Microperineural invasion had a minimum level of $P=0{\cdot}02$ (*Table 2*).

Table 2 Results of multivariate analysis (Cox proportional hazards regression)

Factor	β	Standard error	χ^2	*P*
Gross appearance	0·122	0·607	0·04	0·84
Tumour size	1·219	0·548	4·94	0·03
Pancreatic invasion	2·641	1·482	3·18	0·07
Microperineural invasion	2·085	0·875	5·68	0·02

In the 25 patients the following types of tumour recurrence were observed: lymph node metastasis, nine patients; distant metastases (lung, liver, bone), five patients; local recurrence, two patients; and peritoneal dissemination, seven patients.

Discussion

Ampullary carcinoma is generally resectable and has a more favourable prognosis than other periampullary carcinomas[2,3]. The 5-year survival rate in patients with ampullary carcinoma is reportedly 30–50 per cent[1,18–21] (six of 25 patients in the present series). Some patients with early recurrence have a poor prognosis and have been studied to determine prognostic factors. Tumour diameter, histological type, lymphatic vessel invasion and pancreatic invasion are related to prognosis. As perineural invasion in patients with ampullary carcinoma occurs in only 4·5–17 per cent[22–24], it is not considered a useful prognostic factor. In this study the incidence of microperineural invasion using S-100 staining was significantly higher than that of the perineural invasion with haematoxylin and eosin staining.

As in other studies[11,12,25–27], in the present study tumour gross appearance, diameter, pancreatic invasion and duodenal invasion were significant prognostic factors. With regard to reports[4,8,9] that the presence of lymph node metastases is a prognostic factor, the 5-year survival rate according to the presence or absence of lymph node metastasis was two of nine patients and eight of 16 respectively. This difference was not significant; four patients with metastases had been observed for less than 3 years.

The presence of perineural invasion has been related to prognosis but in studies too small to allow statistical analysis[24,28]. With sufficient patients for multivariate analysis, of factors thought to be related to prognosis microperineural invasion was found to be the most important.

Most patients with pancreatic carcinoma have lymph node metastases, lymphatic vessel invasion and perineural invasion[29]; thus the types of recurrence[30,31] following resection include local recurrence, retroperitoneal lymph node recurrence, liver metastasis and peritoneal dissemination. In the present study, recurrence types after resection of ampullary carcinoma were similar, emphasizing the importance of microperineural invasion in prognosis for both tumours[32,33].

In addition to pancreaticoduodenectomy, operative procedures for ampullary carcinoma now include local resection[34,35], which has a lower morbidity and mortality. However, as duodenal invasion, pancreatic invasion and microperineural invasion were found to be prognostic factors, pancreaticoduodenectomy should remain the procedure of choice for ampullary carcinoma.

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Outcome of palliative biliary and gastric bypass surgery for pancreatic head carcinoma in 126 patients

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Background Recent reports of decreased morbidity and mortality following palliative surgery for patients with irresectable pancreatic head carcinoma prompted a review of the results in 126 patients (median age 64 (range 39–90) years) who had undergone palliative biliary and gastric bypass surgery.

Methods The indication for surgical palliation was the finding of an irresectable tumour at laparotomy ($n=44$), failure of endoscopic treatment ($n=43$), clinical symptoms of gastric outlet obstruction ($n=28$) and miscellaneous ($n=11$). Biliary and gastric bypass was performed in 118 patients, biliary bypass alone in six and gastrojejunostomy alone in two. The indication for gastrojejunostomy was symptoms in 28 patients (23 per cent) and prophylaxis in 92 patients (77 per cent).

Results Postoperative local complications occurred in 17 per cent of patients, general complications in 10 per cent and delayed gastric emptying in 14 per cent of patients. The 30-day mortality rate was 1 per cent and overall hospital mortality rate 2 per cent. Median hospital stay was 17 (range 5–80) days. Median overall postoperative survival was 190 (range 14–830) days. Late obstructive gastrointestinal symptoms occurred in 14 patients (11 per cent) after a median of 141 (range 21–356) days.

Conclusion Roux-en-Y hepaticojejunostomy combined with gastrojejunostomy offers effective palliation for irresectable pancreatic head cancer and can be performed with low mortality and acceptable morbidity rates.

Pancreatic head carcinoma is increasing worldwide[1,2]. At the time of diagnosis, fewer than 20 per cent of patients are amenable to curative resection[1,3–5]. Most patients require some form of palliation. In recent years, the application of palliative surgical procedures has declined owing to the availability of endoscopic procedures for drainage of the biliary tree. Two reasons for this shift towards non-surgical biliary drainage can be identified. First, the number of exploratory laparotomies leading to a palliative biliary and gastric bypass procedure has been reduced as a result of improved preoperative imaging techniques and new diagnostic modalities such as diagnostic laparoscopy[6]. Second, increased endoscopic experience and the development of new types of endoprotheses, such as self-expanding stents, have minimized the failure rate of endoscopic biliary stenting. Historically, biliary bypass surgery has had a high morbidity rate (up to 56 per cent) and mortality rate (up to 33 per cent), leaving little scope for the surgeon in the palliation of patients with incurable pancreatic head carcinoma[7–11].

Recently, improved results of surgical biliary drainage have been reported, with postoperative morbidity rates of 15–37 per cent and mortality rates in the range of 2·5–19 per cent[12–20]. There remains debate about whether to add prophylactic gastroenterostomy to biliary bypass[21–26]. This prompted an analysis of the results of biliary and gastric bypass surgery in 126 patients who were found to have incurable carcinoma of the pancreatic head.

Patients and methods

The records of 126 patients (62 women, 64 men) were reviewed. All had received surgical palliation for irresectable carcinoma of the pancreatic head between 1983 and 1994 The median age of the patients was 64 (range 39–90) years. Symptoms at first presentation and preoperative diagnostic procedures are listed in *Table 1*. Recently, laparoscopy in combination with laparoscopic ultrasonography has been included in the preoperative investigation.

Preoperative biliary drainage was performed in 91 patients (72 per cent), but was not achieved in 35 (*Table 2*). Endoscopic biliary drainage decreased bilirubin levels from a median of 171 (range 33–461) mmol/l to 28 (range 5–371) mmol/l ($P<0{\cdot}05$) before operation. Median preoperative bilirubin level in patients having no preoperative biliary drainage was 26 (range 5–351) mmol/l

Indications for surgical palliation and tumour stage are shown in *Table 3*. Histological confirmation of the diagnosis of adenocarcinoma was obtained in 97 patients (77 per cent) In the remainder (23 per cent) the diagnosis was based on clinical findings and the results of imaging studies.

Biliary bypass was performed routinely in conjunction with gastroenterostomy ($n=118$) (*Table 4*). An isolated hepaticojejunostomy or gastroenterostomy was performed in six and two patients respectively. Biliary bypass has consisted of Roux-en-Y hepaticojejunostomy since 1985 (81 per cent). In the early years of the study, however, various types of biliary bypass were constructed. Side-to-side gastroenterostomy was performed in a retrocolic fashion in 116 patients and in an antecolic fashion in four. Postoperative delayed gastric emptying was defined when

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Table 1 Presenting symptoms and preoperative diagnostic procedures

	No. of patients
Symptoms at first presentation	
Jaundice*	113 (90)
Weight loss†	103 (82)
Pain	60 (48)
Gastric outlet obstruction	28 (22)
Preoperative diagnostic procedures	
ERCP	117 (93)
Ultrasonography	113 (90)
Computed tomography	62 (49)
Duplex ultrasonography	59 (47)
Angiography	34 (27)
Fine-needle aspiration biopsy	13 (10)

Values in parentheses are percentages. *After a median of 19 (range 2–120) days, †median weight loss 7·5 (range 1–32) kg after a median of 2·5 (range 0·5–24) months. ERCP, endoscopic retrograde cholangiopancreatography

Table 2 Preoperative intervention

	No. of patients
Preoperative biliary drainage	91 (72)
Stent*	89
Papillotomy	1
T tube drainage	1
No preoperative biliary drainage	35 (28)
Failure of initial ERCP	24
Duodenal obstruction	20
Perforation	4
Diagnostic ERCP	2
ERCP not performed	9

Values in parentheses are percentages. *A median of one endoprothesis (range 1–5 stents) was inserted for a median interval of 40 (range 10–706) days. ERCP, endoscopic retrograde cholangiopancreatography

Table 3 Indication for surgical palliation and tumour stage

	No. of patients
Indication for surgical palliation	
Irresectable tumour found at exploratory laparotomy	44 (35)
Failure of endoscopic palliation	43 (34)
Failure of initial ERCP	24
Duodenal obstruction	20
Perforation	4
Failure of stent replacement	19
Duodenal obstruction	16
Perforation	3
Symptoms of gastric outlet obstruction	28 (22)
Miscellaneous	11 (9)
Tumour stage*	
Locally advanced tumour†	88 (70)
Metastatic tumour	38 (30)

Values in parentheses are percentages. *Median tumour size at intraoperative assessment was 4·5 (range 1·5–12) cm. †Due to involvement of the portal venous system or major arteries, or infiltration of the mesocolon or retroperitoneum. ERCP, endoscopic retrograde cholangiopancreatography

Table 4 Types of biliary and gastric bypass

	No. of patients
Surgery	
Biliary bypass combined with gastroenterostomy	118 (94)
Biliary bypass alone*	6 (5)
Gastroenterostomy alone†	2 (2)
Type of biliary bypass	
Hepaticojejunostomy	100 (80)
Hepaticoduodenostomy	2 (2)
Cholecystojejunostomy	6 (5)
Cholecystoduodenostomy	1 (1)
Hepaticogastrostomy	2 (2)
Cholecystogastrostomy	13 (10)
Gastroenterostomy performed	
For symptoms	28 (23)
Prophylactically	92 (77)

Values in parentheses are percentages. *For reasons of brief life expectancy or surgeon's preference; †one patient had percutaneous biliary drainage and the other had a tumour in the neck of the pancreas without biliary obstruction

Table 5 Postoperative morbidity, mortality and hospital stay

	No. of patients
Morbidity*	
Local complications	22 (17)
Gastrointestinal bleeding	8
Wound infection	8
Intra-abdominal abscess	6
General complications	12 (10)
Urinary tract infection	7
Pneumonia	3
Decubitus ulcer	1
Neuropathy of the peroneal nerve	1
Delayed gastric emptying*†	18 (14)
After gastroenterostomy for symptoms	7
After prophylactic gastroenterostomy	11
Mortality*	
Hospital mortality	3 (2)
30-day mortality	1 (1)
Median (range) hospital stay (days)	17 (5–80)

*Values in parentheses are percentages. †Median duration of nasogastric suction was 9 (range 1–39) days and/or a normal diet was tolerated after a median interval of 14 (range 11–41) days

nasogastric suction was required for more than 7 days and/or a normal diet was not tolerated within 10 days of surgery

Statistical analysis was performed with the non-parametric Mann–Whitney *U* test, χ^2 test or log rank test. Survival analysis was with the Kaplan–Meier method. $P<0{\cdot}05$ was considered statistically significant.

Results

Data on postoperative morbidity and mortality are listed in *Table 5*. The overall postoperative complication rates in 91 patients who had preoperative endoscopic drainage and in 35 who did not receive an endoprothesis were 23 per cent and 37 per cent respectively ($P=0{\cdot}2$). Hospital mortality rate was no different in the two groups (2 and 3 per cent, $P=0{\cdot}59$). Age and tumour size did not correlate with the overall postoperative complication rate ($P=0{\cdot}59$

Table 6 Follow-up after biliary and gastric bypass surgery for irresectable pancreatic head carcinoma in 126 patients

Median (range) overall postoperative survival (days)*	190 (14–830)
6-month survival rate (%)	
Local tumour	67
Metastatic tumour	24†
1-year survival rate (%)	
Local tumour	20
Metastatic tumour	3‡
No. of readmissions (%)	18 (14)
Terminal care	8
Late obstructive gastrointestinal symptoms	8
Peritoneal metastases	1
Pain management	1

*Median survival outside hospital 172 (range 0–805) days. †$P = 0{\cdot}0005$, ‡$P = 0{\cdot}015$ (metastatic *versus* local tumours, log rank test)

and $P = 0{\cdot}73$ respectively), nor with hospital mortality (all postoperative deaths occurred in patients under the age of 70 years and with a tumour diameter of less than 5 cm). The occurrence of postoperative complications increased hospital stay significantly from a median of 15 (range 6–24) days to 25 (range 5–80) days ($P < 0{\cdot}05$).

Postoperative follow-up data are shown in *Table 6*. Median postoperative survival in patients with locally advanced tumours and in those with metastatic disease was 226 and 98 days respectively ($P < 0{\cdot}0001$) (*Fig. 1*). Postoperative survival in patients who underwent surgical palliation after failed endoscopic treatment was 158 days ($P = 0{\cdot}61$). No correlation was found between postoperative survival and age ($P = 0{\cdot}69$) or tumour size ($P = 0{\cdot}58$). Median postoperative survival was similar in patients lacking histological confirmation of the tumour and in those with a histologically proven pancreatic carcinoma (147 and 190 days respectively, $P = 0{\cdot}22$).

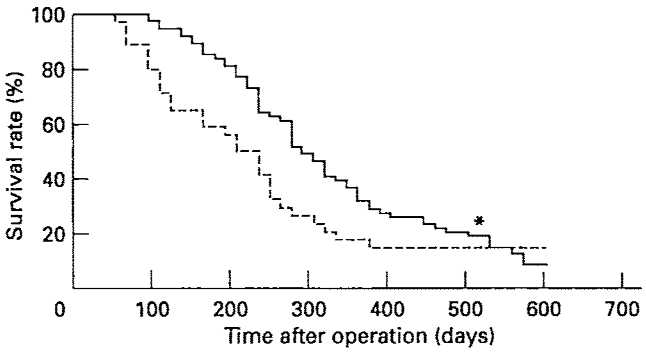

Fig. 1 Postoperative survival in patients who had biliary and gastric bypass for locally advanced tumours (—, $n = 88$) or metastatic disease (– – – –, $n = 38$). Hospital mortality (within 30 days) was excluded from the analysis. *$P < 0{\cdot}0001$ (local *versus* metastatic tumours, log rank test)

Development and treatment of late obstructive gastrointestinal symptoms in 14 patients (11 per cent) is described in *Table 7*. In 120 patients who had a gastroenterostomy, the risk of late obstructive gastrointestinal symptoms was significantly higher when the procedure had been done for symptoms rather than for prophylaxis ($P < 0{\cdot}05$, log rank test). In patients who had a prophylactic gastroenterostomy, the risk of late obstructive gastrointestinal symptoms was no different between local irresectable and metastatic pancreatic carcinoma ($P = 0{\cdot}46$).

Discussion

Several studies have compared surgical palliation with non-operative biliary drainage for malignant obstructive jaundice[21,27–31]. Although equally effective in relief of jaundice, biliary bypass has generally been associated with more early complications and a higher procedure-related mortality rate than endoscopic palliation. More late complications, however, have been reported following endoscopic treatment: stent occlusion requiring frequent stent exchanges, and duodenal obstruction. With respect to long-term survival, no clear advantage of either mode of palliation has been reported. The present analysis of 126 patients shows that surgical palliation for irresectable pancreatic carcinoma can be performed with an overall hospital mortality rate of 2 per cent and a morbidity rate of 27 per cent. Morbidity was similar to that reported in more recent studies, whereas the mortality rate was even lower[12–20]. The majority (72 per cent) of patients had preoperative biliary drainage, although, as previously reported[32], no significant reduction in the number of postoperative complications was noted in this group.

In 34 per cent of patients in this study, palliative surgery was done because initial endoscopic treatment had failed. Reasons for endoscopic failure were duodenal obstruction or anatomical anomalies precluding access to the papilla of Vater, or intestinal perforation. Many of these patients were previously deemed at too high a risk to undergo surgery for reasons of age, tumour size,

Table 7 Management and survival of 14 patients with late obstructive gastrointestinal symptoms a median of 141 days after initial palliative surgery

	No gastroenterostomy ($n = 6$)	Prophylactic gastroenterostomy ($n = 92$)	Gastroenterostomy for symptoms ($n = 28$)	Median (range) survival (days)
Management				
Surgical*	2	1	2	46 (21–356)
Non-surgical†	0	7	2	14 (5–104)
Total	2	8	4	19 (5–356)
Median (range) interval before onset of symptoms (days)	97 (94–100)	183 (21–356)	133 (69–216)	

*Local recurrence was found in one patient and peritoneal metastases in four, for which gastroenterostomy or enteroenterostomy was performed; †three patients were readmitted for conservative treatment and six received only medical support at home general condition or limited life expectancy. Despite these contraindications, the surgical procedures were tolerated well by most patients, with satisfactory results. Similarly, no relation between age or tumour size and postoperative morbidity or mortality could be demonstrated, contrary to reports in the literature[31].

The addition of a gastroenterostomy to biliary bypass to prevent gastric outlet symptoms is controversial[21–26]. The incidence of gastric outlet obstruction in patients having only a biliary bypass has been reported to be 3–50 per cent[23]. In a series of 691 patients with irresectable tumours in the region of the pancreatic head treated by endoscopic palliation in the authors' institution, 11 (range 9–26) per cent developed duodenal obstruction after a median of 5 months[33]. Duodenal obstruction was strongly related to length of survival and was commonest in patients with ampullary carcinoma. In the present study, prophylactic gastroenterostomy was performed routinely with biliary bypass. This did not add to morbidity and mortality, especially delayed gastric emptying, in contrast with other reports[23]. In the present series, no risk factors for the development of late obstructive gastrointestinal symptoms could be identified. Sarr *et al.*[25] have suggested that patients with liver metastases are less likely to benefit from prophylactic gastroenterostomy. One such patient in the present series, however, developed late obstructive gastrointestinal symptoms and needed reoperation. Overall, late obstructive gastrointestinal symptoms developed in 11 per cent of patients, as a result of peritoneal metastases in most cases. Late obstructive symptoms in these patients appeared to be a terminal event, with brief survival regardless of surgical intervention. This experience with the creation of a prophylactic gastroenterostomy is consistent with a recent prospective study showing that concomitant gastric bypass reduces the number of late symptoms and reoperations, without increasing mortality[21].

Optimal management of patients with irresectable pancreatic carcinoma encompasses palliation of three major symptoms: obstructive jaundice, duodenal obstruction and pain[14]. Endoscopic treatment can relieve jaundice, but surgical treatment can treat all three. A biliary–digestive anastomosis is a solution to the problem of biliary obstruction and can be performed with low mortality and acceptable morbidity rates, even in high-risk patients. Because the long-term results of hepaticojejunostomy are better than those of cholecystojejunostomy[3], the authors now almost exclusively perform Roux-en-Y hepaticojejunostomy for biliary bypass. The surgical palliative procedure is completed with coeliac plexus injection of 50 per cent alcohol, an effective measure to relieve pain[20].

The decision to carry out surgical or non-surgical palliation in patients with irresectable pancreatic carcinoma is presently based on the results of preoperative investigation. In this institution, diagnostic procedures include ultrasonography with Doppler evaluation of the portal venous system, spiral computed tomography and diagnostic laparoscopy combined with laparoscopic ultrasonography. In 19 per cent of cases, it is possible to prevent unnecessary laparotomy using diagnostic laparoscopy combined with laparoscopic ultrasonography. These patients are palliated with biliary endoprothesis[6]. During long-term follow-up, 15 per cent of these patients required a later laparotomy for duodenal obstruction[34]. Until now, the question of whether patients should be treated surgically or endoscopically when diagnostic laparoscopy reveals an irresectable tumour has not been answered. The authors have started a randomized trial to compare the results of surgical *versus* endoscopic palliation in these patients.

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Endoscopic mechanical lithotripsy of difficult common bile duct stones

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Background Mechanical lithotripsy for the management of difficult common bile duct stones has sometimes yielded conflicting results.
Methods A series of 162 consecutive patients who underwent mechanical lithotripsy was evaluated retrospectively and a large number of variables tested for their association with successful outcome.
Results The procedure was safe (morbidity rate 1·8 per cent) and effective (84·0 per cent stone clearance rate). Univariate and multivariate analysis showed that stone size was the only outcome predictor (mean(s.d.) diameter of grasped *versus* non-grasped stones 21·7(6·7) *versus* 28·3(10·4) mm; $F = 10{\cdot}72$, 98 d.f., $P = 0{\cdot}002$) The cumulative probability of bile duct clearance ranged from over 90 per cent for stones with a diameter less than 10 mm to 68 per cent for those greater than 28 mm in diameter ($P < 0{\cdot}02$).
Conclusion Patients at high risk of lithotripsy failure (stone diameter of 28 mm or more) might more wisely undergo surgery or other non-surgical procedures, such as extracorporeal shock-wave lithotripsy or long-term biliary stenting.

Endoscopic mechanical lithotripsy is an established procedure for dealing with 'difficult' common bile duct (CBD) stones, being regarded as the option of choice when stone extraction with Dormia basket or balloon catheter following endoscopic sphincterotomy has failed. With standard extraction techniques, the common duct can be cleared of stones in about 90 per cent of cases[1,2]; mechanical lithotripsy can provide a further therapeutic gain of 4–8 per cent[3–5], although widely variable success rates have been reported, ranging from 51 to 100 per cent[5–19]. These discrepancies might be explained partially by the different influence that various factors had over the efficacy of this treatment in different series, mainly the stone size, but also the CBD configuration, the type of lithotriptor employed and, occasionally, stone hardness[9,17].

The present report aimed to identify variables predictive of success of mechanical lithotripsy in order to characterize better patients who are more likely to benefit from the procedure.

Patients and methods

Clinical and endoscopic records of all patients treated by sphincterotomy and attempted stone extraction for suspected choledocholithiasis from August 1988 to December 1994 were collected on to a computer database. Of a total of 1722 consecutive patients, precut papillotomy was necessary in 224 cases (13·0 per cent) and percutaneous transpapillary guidance in 14 (0·8 per cent) Balloon dilatation of the sphincter before lithotripsy was performed only once in the present series, for a severe coagulopathy. Overall, 162 patients (9·4 per cent) had CBD stones that could not be extracted with standard techniques. In these patients mechanical lithotripsy was attempted during the same endoscopic session.

There were 47 men and 115 women with a mean(s.d.) age of 69·1(13·1) (range 29–90) years. Seventy-four patients had the gallbladder *in situ*. On cholangiography, 58 patients had single stones and 104 had multiple stones, ranging in size from 9 to 50 (mean(s.d.) 22·7(7·3)) mm. Thirty-two patients underwent an emergency procedure (*Table 1*). CBD clearance had failed in these patients because the stone size exceeded the sphincterotomy (130 patients (80 per cent)), the stones were proximal to a narrowed or S-shaped biliary tract (20) or the papilla was located in a diverticulum which limited the size of the papillotomy (12).

Treatment was accomplished using Olympus BML-1Q, BML-2Q and BML-4Q intraendoscopic systems (Olympus Optical, Hamburg, Germany) or a Soehendra-type Wilson–Cook SLS-2 extraendoscopic lithotriptor (Cook, Limerick, Ireland), as described previously[11]. Repeated attempts (up to three) were performed in case of failure of the first treatment.

For the purpose of the study, the impact of the following variables on the outcome of the procedure was tested. age and sex of patients, CBD morphology (normal *versus* S-shaped or narrowed), presence of peripapillary diverticula, previous Billroth II gastrectomy, clinical picture, timing of lithotripsy (elective or emergency), number and size of stones, type of lithotriptor employed (intraendoscopic or extraendoscopic) and the number of attempts at crushing stones.

Statistical analysis

Data were processed using the SPSS/PC version 4 11 statistical package (M. J. Norusis, Chicago, Illinois, USA) Comparison

Table 1 Characteristics of 162 patients who underwent endoscopic mechanical lithotripsy

	No. of patients
No. of stones	
1	58 (36)
2	79 (49)
>2	25 (15)
Periampullary diverticula	20 (12)
Previous Billroth II gastrectomy	11 (7)
Emergency treatment (cholangitis, pancreatitis)	32 (20)

Values in parentheses are percentages

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between continuous variables was performed using variance analysis; comparison between discrete variables was with the χ^2 test and Fisher's exact test, when appropriate Multivariate analysis was carried out by the discriminant analysis method. $P < 0.05$ was regarded as statistically significant.

Results

Complete clearance of the CBD was obtained in 136 patients (84·0 per cent) Of these, 119 patients were cleared successfully during the initial attempt, whereas 17 required multiple treatments (11 patients two sessions, five patients three and one patient four). These patients received a temporary biliary stent between procedures. Once grasped, all the stones could also be fragmented easily. Subsequent open or laparoscopic cholecystectomy was performed in 53 patients, whereas endoscopic sphincterotomy and lithotripsy was the definitive treatment in 21 considered unfit for surgery because of advanced age or poor surgical risk. There were no deaths after lithotripsy. Procedure-related morbidity occurred when there was inadequate biliary drainage and consisted of three cases of cholangitis (1·8 per cent), all successfully managed with surgery. Hyperamylasaemia occurred in 36 patients (22·2 per cent), with two (1·2 per cent) developing clinical pancreatitis, which subsided with conservative therapy.

Table 2 Univariate analysis of variables predictive of the outcome of endoscopic mechanical lithotripsy

Variable	Clearance	Failure	*P*
Mean(s.d) age (years)*	69 3(13·5)	66 6(7·8)	0·60
Sex†			
Male	76		0 34
Female	86		
Previous Billroth II gastrectomy†			
Yes	73		0·54
No	85		
Peripapillary diverticula†			
Yes	78		0·08
No	86		
CBD stenosis or tortuosity†			
Yes	80		0 09
No	84		
Type of lithotriptor†			
Olympus	82		0 40
Soehendra	88		
No. of stones†			
1	81		0·88
2	82		
>2	100		
Mean(s d) no. of stones*	2·0(1·3)	1·8(1·4)	0·62
No. of attempts†			
1	82		0·74
2	88		
>2	100		
Clinical picture†			
Jaundice	87		0·73
Abdominal pain	76		
Cholangitis	85		
Other	86		
Mean(s d.) stone size (mm)*	21·7(6·7)	28·3(10·4)	0·002
Emergency treatment†			
Yes	84		1·0
No	83		

Values are percentages unless indicated otherwise. CBD, common bile duct. *Analysis of variance; †χ^2 and Fisher's exact tests

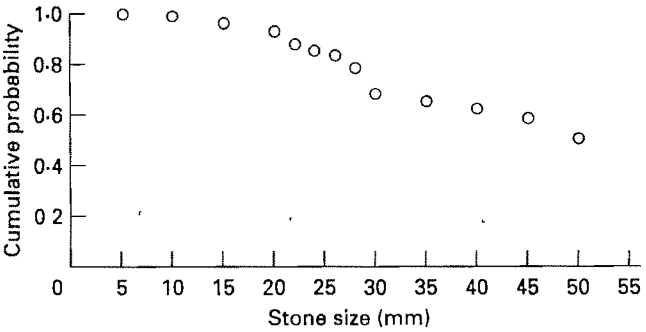

Fig. 1 Cumulative probability of common bile duct clearance according to stone size. $P < 0.02$ (stone diameter less than 22 mm *versus* greater than 28 mm, discriminant analysis)

Mechanical lithotripsy failed in 26 patients (16·0 per cent), mostly due to inability to capture the stone within the basket (24 of 26 cases). Further management of these patients involved operative and non-operative therapy. Open CBD exploration with or without T tube drainage was accomplished in 14 patients, three of whom also had bilioenteric drainage (two choledochoduodenostomy, one Roux-en-Y choledochojejunostomy). Surgical clearance of the bile duct was achieved in all 14 patients, and one patient died from multiple organ failure 13 days after surgery. Postoperative morbidity consisted of one biliary fistula which was managed with endoscopic stenting. Twelve patients received non-operative treatment: extracorporeal shock-wave lithotripsy (ESWL) ($n = 8$), intracorporeal electrohydraulic lithotripsy ($n = 2$) and definitive biliary stenting ($n = 2$). These last two patients achieved adequate biliary drainage without complications at 13 and 18 months.

On univariate analysis, stone size was found to be the only variable that could differentiate successful treatment from failure: the mean(s.d.) diameter of extracted stones was 21·7(6·7) mm, whereas that of non-grasped stones was 28·3(10·4) mm ($F = 10{\cdot}72$, 98 d.f., $P = 0{\cdot}002$) (*Table 2*). Discriminant analysis showed that the size of stones was the single predictive variable to differentiate successful from unsuccessful lithotripsy. None of the variables previously identified as not significant was able to provide any improvement to the final model. The cumulative probability of CBD clearance ranged from over 90 per cent for stones with a diameter of less than 10 mm to 68 per cent for stones greater than 28 mm and to a dismal 50 per cent for stones of 50 mm (*Fig. 1*).

Discussion

Since the description by Demling *et al.*[20] in 1982, endoscopic mechanical lithotripsy has been accepted as the most reliable method of crushing difficult CBD stones, significantly improving the success rate of endoscopic extraction[21]. This review of mechanical lithotripsy performed in 162 patients with an overall success rate of 84·0 per cent and a specific complication rate of 1·8 per cent once again confirms the efficacy and safety of the procedure[2,5–19,22].

Despite the pitfalls of a retrospective study, the authors tried to identify factors potentially affecting the outcome of lithotripsy, so as to improve the selection of candidates for the procedure. Reasons for failure of this technique may be the inability to grasp a large and/or occluding (wall to wall) stone as well as a stone located in or above a sigmoid or narrowed CBD, preventing the progression or the complete unfolding of the basket[1,5,10]. Other technical problems such as rupture of the basket or impaction of the lithotriptor may occasionally account for failure of mechanical lithotripsy[9]. However, apart from stone size, this analysis showed that none of these factors had any role in determining the outcome of the procedure; neither had any other variables such as age, sex, clinical picture, duodenal diverticula, previous Billroth II gastrectomy, number of stones or type of lithotriptor used.

Stone hardness does not seem to represent a limiting factor for mechanical lithotripsy, as in the present series all grasped stones could also be fragmented successfully. Stone size has already been reported as an important predictor of success or failure of lithotripsy[18,22], but in the present study it was the only outcome predictor, likely to represent the key factor accounting for such remarkable differences in the success rate of mechanical lithotripsy quoted by different groups.

Considering the increased morbidity rate associated with repeated intraductal manipulation, the risk of cholangitis if lithotripsy fails and the likely poor compliance of the patient to multiple lithotripsy sessions, it would seem wiser for patients at 'high risk' of mechanical lithotripsy failure (those with stone diameters of 28 mm or more) to undergo other procedures once the first crushing attempt has failed or even to be treated primarily with different therapeutic options, such as ESWL or biliary stenting. ESWL proved to be safe and effective independently of stone size[23], as confirmed in eight patients in the present series. Permanent biliary stenting in patients with irretrievable CBD stones may be an alternative to ESWL in elderly patients at poor surgical risk, unfit for elective treatment and with a short life expectancy. It should be used selectively as late complications occur in 20–40 per cent of cases and this risk increases proportionally with time[24,25]. Finally, the safety of modern surgical techniques must not be overlooked in this setting.

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Reduction of intraperitoneal adhesion formation by use of non-abrasive gauze

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Background Adhesion formation is potentially harmful. Surgical swabs may contribute to adhesions by trauma to the peritoneum. The purpose of this study was to evaluate whether standard surgical gauze (Medipres) has an adhesion-promoting effect, and to determine whether a soft textile (Fastsorb), used in the electronics industry, might be less traumatic and therefore lead to less adhesion formation.

Methods A reproducible rat model allowing semiquantitative scoring of adhesion formation was used. Three different adhesion models representing increasing degrees of peritoneal trauma (minimal, moderate and severe) were employed. The model inflicting minimal peritoneal trauma was combined with standardized rubbing of the peritoneum with surgical gauze or non-surgical textile.

Results Minimal peritoneal trauma resulted in a significantly lower mean adhesion percentage (21 per cent) than moderate (44 per cent) or severe (60 per cent) peritoneal trauma ($P \leq 0{\cdot}005$). Rubbing of the peritoneum with surgical gauze after minimal peritoneal trauma induced significantly more adhesion formation (58 *versus* 23 per cent, $P < 0{\cdot}0001$). After minimal peritoneal trauma, rubbing with surgical gauze produced significantly more adhesions than rubbing with non-surgical textile (63 *versus* 19 per cent, $P < 0{\cdot}0001$). Moreover, rubbing the peritoneum with non-surgical textile after minimal peritoneal trauma did not induce any additional adhesion formation (35 *versus* 24 per cent, $P = 0{\cdot}23$).

Conclusion The extent of adhesion formation correlates significantly with the degree of peritoneal damage. Standard surgical gauze is traumatizing to the peritoneum and promotes adhesion formation whereas a less abrasive non-surgical textile does not.

Postoperative adhesions are abnormal unions between tissue surfaces which occur after almost every intra-abdominal surgical intervention and can lead to a number of complications. Adhesion formation after intra-abdominal surgery accounts for 70–90 per cent of all adhesions[1–3], the rest being caused by inflammation of the peritoneum, endometriosis (18 per cent) and congenital adhesions (2·8–6 per cent)[4]. Abdominal adhesions can cause intestinal obstruction which often requires immediate surgical intervention. Thirty per cent of all bowel obstructions are caused by postoperative adhesions[5–8]. About 1 per cent of all surgical admissions and 3 per cent of all laparotomies are done for intestinal obstruction due to adhesions[7]. The mortality rate from intestinal obstruction due to adhesions is 6–8 per cent[1,2,4]. Some 15–20 per cent of infertility in women is a consequence of adhesion formation[9–13] and adhesions were identified as the primary cause of chronic pelvic pain in 13–26 per cent of female patients[14,15].

A wide variety of therapeutic modalities to reduce the incidence of postoperative adhesion formation has been studied in clinical and experimental work. The results achieved with the different treatment modalities are inconsistent and associated with many side-effects such as intra-abdominal haemorrhage and impaired wound healing. Until now only one strategy existed to reduce adhesion formation, namely the reduction, at operation, of all forms of peritoneal trauma and ischaemia. This necessitates avoiding desiccation and vigorous handling of intra-abdominal tissues, and introducing as little foreign material as possible[16–18].

Manipulation with abdominal gauze might be traumatic to the peritoneum either because it is rough and abrades the peritoneum and serosa or because remnants of gauze are left behind in the abdomen[19,20]. The present study was undertaken to evaluate whether a soft textile used in the electronics industry might have a less traumatic effect on the peritoneum than standard surgical gauze, and consequently lead to less adhesion formation. A reproducible animal model was used that allowed semiquantitative scoring of adhesion formation.

Materials and methods

Animals

Female Wistar rats of reproductive age weighing 200–250 g were obtained from Harlan, Zeist, The Netherlands They were bred under specific pathogen-free conditions and kept under standard laboratory conditions (temperature 20–24°C, relative humidity 50–60 per cent, 12 h light and 12 h dark). The rats were given standard rat food and water *ad libitum*. The experimental protocol adhered to rules laid down by the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of Erasmus University, Rotterdam.

Gauzes

The evaluated 'gauzes' were surgical Medipres (van Heek Medical, Losser, The Netherlands) gauze, consisting of 100 per cent cotton and commonly used in abdominal surgery, and non-surgical Fastsorb (Berkshire Corporation, Great Barrington, Massachusetts, USA) cleanroom wiper, used in the electronics industry. Fastsorb is a rayon–polyester blend which possesses strength and softness combined with a high absorbing capacity. It has low particle generation, minimal extractable matter and a low ion content. Fastsorb is used on abrasion-sensitive surfaces.

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Absorbing capacity The absorbing capacity of both materials was evaluated using the following method. Ten 5×5-cm pieces of surgical Medipres gauze (double layer) and non-surgical Fastsorb textile (monolayer) were saturated by immersion in water. After saturation the materials were drained for 30 s. The pieces were weighed before and after saturation; results were expressed in millilitres of water absorbed per gram of gauze.

Surgical techniques

The three adhesion models employed in this study were derived from a model described by van Bakkum *et al.*[21].

Model 1. Under ether anaesthesia and aseptic but not sterile conditions, using Biogel sterile gloves (Regent Hospital Products, London, UK), the abdomen was shaved and cleaned with alcohol. Laparotomy was performed using a lower midline incision of 5 cm. In the lateral abdominal wall, 1·5 cm downwards from the abdominal incision, a standard area of 1·5×1·2 cm, 3-mm deep, which contained the mesothelial as well as both underlying muscular layers, was excised with an oval-shaped punch This severe peritoneal defect was then closed with three 5/0 Surgilene sutures (Braun, Melsungen, Germany). Subsequently the uterine horn was sutured to the lateral peritoneum, both proximally and distally to the closed peritoneal defect, with 6/0 Surgilene. All knots were double knots fastened tightly to ensure ischaemia. The abdomen was closed in two layers with 5/0 polyglycolic acid and 2/0 silk sutures

Model 2. The same type of operation was performed with only one difference· the damage inflicted on the lateral peritoneum was of moderate severity and consisted only of an incision of 1·5 cm, 3-mm deep, which was also closed with three 5/0 Surgilene sutures.

Model 3. In this model minimal trauma to the lateral peritoneum was applied. No wound was inflicted. The trauma was ischaemic only and was brought about by three tight 5/0 Surgilene sutures at 0·7-cm intervals.

Rubbing with surgical gauze and non-surgical textile was done with a device enabling the application of a constant pressure of 120 g/cm^2 (*Fig. 1*) The uterine horn was rubbed ten times over its total length.

Experimental design

Adhesion formation after different amounts of peritoneal trauma. In 15 rats one lateral abdominal wall side was operated on according to adhesion model 1 (severe peritoneal trauma). In nine of these animals the other side was treated according to adhesion model 2 (moderate peritoneal trauma) and six were treated according to adhesion model 3 (minimal peritoneal trauma).

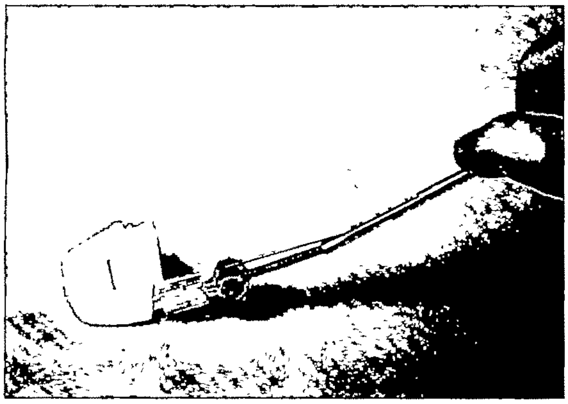

Fig. 1 Rubbing device used to apply standardized trauma to the uterine horn. A spring attached to the handle enables rubbing under a certain pressure The device is constructed in such a manner that a pressure of 120 g/cm^2 is applied when the indicator needle (above the spring) touches the blue roll. The gauze is wrapped and fixed around a hooked injection needle (1·1×40-mm Luer-Lock; Braun, Melsungen, Germany)

Adhesion formation in model 3 after rubbing with surgical gauze and non-surgical textile. In 30 rats minimal peritoneal trauma was inflicted at both lateral peritoneal sides (model 3). Both uterine horns were exposed and sutured to the lateral peritoneum. In ten rats one uterine horn was rubbed with surgical Medipres gauze whereas the other one was not touched; in ten animals one uterine horn was rubbed with Medipres gauze and the other with non-surgical Fastsorb textile, and in the last ten rats one uterine horn was rubbed with Fastsorb textile while the other was not touched. In all cases randomization was used to determine which rubbing model was to be carried out on which side

Evaluation of adhesion formation

Some 14 days after operation the rats were killed by a humane method for assessment of postsurgical adhesion formation. Macroscopically the adhesions were scored according to their extent (quantity) and type (quality) by two independent observers. The extent of adhesion formation was quantified by dividing the area to be scored into eight by means of the three sutures by which the defect was closed (*Fig. 2*). The presence or absence of adhesions in each area was scored. If there were

Table 1 Macroscopic (morphological) classification of abdominal adhesions according to Zühlke *et al.*[22]

Zuhlke type	Characteristics
1	Filmy adhesion, easy to separate by blunt dissection
2	Stronger adhesion; blunt dissection possible, partly sharp dissection necessary; beginning of vascularization
3	Strong adhesion; lysis possible by sharp dissection only; clear vascularization
4	Very strong adhesion; lysis possible by sharp dissection only; organs strongly attached with severe adhesions; damage of organs hardly preventable

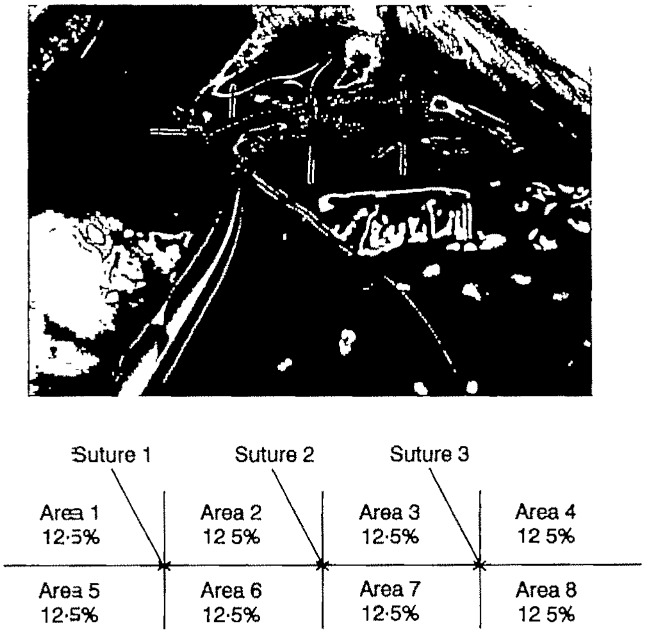

Fig. 2 The extent of adhesion formation was quantified by dividing the 'defect' area to be scored into eight areas of 12·5 per cent by means of the three sutures used to close the defect

adhesions in an area this accounted for 12·5 per cent adhesions; a maximum of 100 per cent adhesions could be scored. In each rat two defected lateral peritoneal sides (two uterine horns) were assessed. The type of adhesions formed was classified macroscopically as described by Zühlke *et al.*[22] (*Table 1*).

Evaluation of peritoneal damage

Microscopic analysis of peritoneal reaction after rubbing ten times with surgical Medipres gauze and non-surgical Fastsorb textile was performed. Peritoneal reaction was evaluated directly after, and 2 and 4 h after rubbing the uterine horn. For each timepoint one-third of the four rubbed uterine horns (two rubbed with Medipres and two with Fastsorb) were excised and fixed in formalin. The samples were stained with haematoxylin and eosin. The degree of disappearance of the mesothelial and underlying muscular layers and infiltration of leucocytes at the damaged surfaces were estimated.

Statistical analysis

Statistical analysis was performed with the t test for paired samples. In two instances the unpaired Student's t test for independent samples was used, as indicated in the text. Statistical significance was defined as $P<0{\cdot}05$. Data were expressed as mean(s.d.) adhesion percentage.

Results

Gauzes: absorbing capacity

The mean(s.d.) absorbing capacity of non-surgical Fastsorb textile ($n=10$) was 8·4(0·2) ml per g gauze and that of surgical Medipres gauze ($n=10$) was 6·6(0·6) ml/g. This difference was statistically significant ($P<0{\cdot}0001$, Student's t test for independent samples).

Table 2 Mean adhesion percentages and Zuhlke classification of adhesions found after severe (model 1), moderate (model 2) and minimal (model 3) peritoneal trauma

Abdominal trauma	'*n*	Percentage adhesions*	Zuhlke type
Model 1	15	60(12·7)†	2–3
Model 2	9	44(15·5)‡	2
Model 3	6	21(6·5)	1–2

*Values are mean(s.d.). Fifteen rats underwent operation in which one lateral abdominal wall side was operated on according to adhesion model 1. In nine of these rats the other, opposite, side was operated on according to model 2, and in six the operation was according to model 3. Therefore, n is the number of peritoneal sides (uterine horns) assessed. †$P=0{\cdot}11$ (model 1 *versus* model 2, $n=9$), $P=0{\cdot}005$ (model 1 *versus* model 3, $n=6$) (t test for paired samples); ‡$P=0{\cdot}004$ (model 2 ($n=9$) *versus* model 3 ($n=6$), Student's t test for independent samples)

Adhesion formation after inflicting different amounts of peritoneal trauma

Adhesion formation was found after 2 weeks on almost all peritoneal defects. No pathological conditions such as bowel obstruction, peritonitis or abscess were found. *Table 2* shows that significantly more adhesions were found at sites where severe (model 1) trauma had been applied, compared with moderate (model 2) and minimal (model 3) peritoneal trauma. Adhesions formed after severe and moderate traumatization of the peritoneum were dense and thick (Zühlke type 2–3). The pelvic fat and uterine horn were involved in adhesion formation. Adhesions formed after minimal traumatization of the peritoneum were filmy and could be classified as Zühlke type 1–2. Only pelvic fat was involved in adhesion formation.

Adhesion formation in model 3 after rubbing with surgical gauze and non-surgical textile

Table 3 shows that rubbing the uterine horn with surgical Medipres gauze after minimal peritoneal trauma gave rise to a significantly higher mean adhesion percentage than minimal peritoneal trauma alone on the opposite side ($P<0{\cdot}0001$). The adhesions in the latter group were often filmy (Zühlke type 1–2) involving only pelvic fat. Adhesions at sites also rubbed by Medipres gauze were denser (Zühlke type 2–3); pelvic fat, the uterine horn and the bowel were involved in these adhesions.

Table 3 shows that, after minimal peritoneal trauma, rubbing the uterine horn with surgical Medipres gauze induced a significantly higher mean adhesion percentage than rubbing with non-surgical Fastsorb textile ($P<0{\cdot}0001$). The adhesions formed after rubbing with Medipres gauze were more dense than those formed after rubbing with Fastsorb textile. In the first group the uterine horn, the bowel and pelvic fat were involved in adhesion formation, whereas in the Fastsorb group the bowel was never involved and the uterine horn rarely.

The mean adhesion percentage found after minimal peritoneal trauma did not differ significantly from that observed after combining this minimal trauma with rubbing the uterus with non-surgical Fastsorb textile ($P=0{\cdot}23$). The adhesions found were all filmy, Zühlke type 1 in the first group and type 1–2 in the second group; only pelvic fat was involved in adhesion formation.

Light microscopy

In all cases the surface of the uterine peritoneum was more damaged after rubbing with surgical Medipres gauze than with non-surgical Fastsorb textile. After rubbing with Medipres, the mesothelial layer had disappeared and the underlying muscular layer was partly lost and looked

Table 3 Mean adhesion percentages and Zuhlke classification of adhesions found after minimal peritoneal trauma alone (uterine horn not touched) or rubbing the horn with Medipres gauze or Fastsorb textile following minimal peritoneal trauma

Uterine horn	*n*	Percentage adhesions*	Zuhlke type	*P*†	95 per cent c.i.
No touching	10	23(9·9)	1–2	<0·0001	−43·2 to −26·8
Medipres rubbing	10	58(10·5)	2–3		
Medipres rubbing	10	63(11·8)	2–3	<0·0001	34·1–53·4
Fastsorb rubbing	10	19(12·2)	1–2		
No touching	10	24(11·6)	1	0·23	−35·8–13·6
Fastsorb rubbing	10	35(24·3)	1–2		

*Values are mean(s.d.); n is the number of peritoneal sides (uterine horns) assessed. c.i., Confidence interval. †t test for paired samples

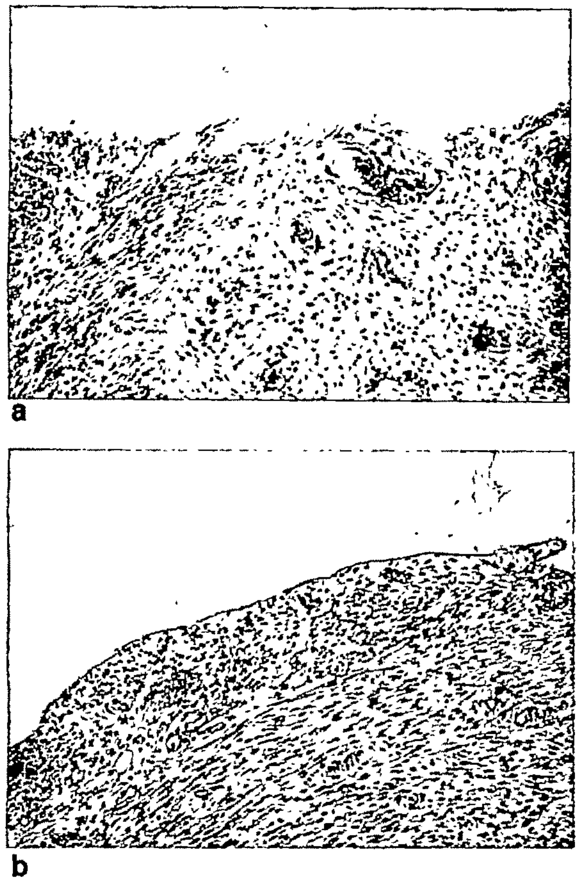

Fig. 3 Light micrograph of the surface of the uterine horn after rubbing with a Medipres gauze and b Fastsorb textile. a The mesothelial layer has disappeared; the underlying muscular layer is partly lost and looks frayed. Reactive leucocyte cells infiltrate the severely damaged surface area. b The mesothelial layer has disappeared for the most part but the underlying muscular layer is intact

frayed. After rubbing with Fastsorb textile, the mesothelial layer had disappeared for the most part but the underlying muscular layer looked smooth and was intact. At 2 and 4 h after causing peritoneal damage with Medipres there were more leucocytes infiltrating the severely damaged area than after rubbing with Fastsorb (*Fig. 3*).

Discussion

Numerous attempts in clinical and animal studies to prevent or reduce the incidence of intraperitoneal adhesions have yielded limited success.

Adhesion formation is a dynamic process consisting of several consecutive stages following damage to the parietal or visceral peritoneum. Different studies, in which peritoneal trauma was proven to be a cause of adhesion formation[21–25], did not mention whether there was a connection between the degree of trauma and the extent of adhesions. The present study shows that the extent and type of postsurgical adhesion formation correlates significantly with the degree of peritoneal damage. At sites where severe, moderate or minimal peritoneal trauma was inflicted, mean adhesion percentages of 60, 44 and 21 per cent respectively were subsequently found.

Damage to the peritoneum produces a local inflammatory reaction which leads to the formation of a serosanguineous exudate[23–26]. In the exudate, fibrin deposition will take place[25–27], and when two surfaces contact each other during this process a fibrinous adhesion will appear. Whether these adhesions are permanent or will eventually be lysed is dependent on the fibrinolytic capacity of the peritoneum[25,28–31]. When the peritoneum is slightly damaged and mesothelial cells are mostly intact, there will be a dynamic balance between fibrinogenesis and fibrinolysis, and adhesion-free healing may take place. When the peritoneum is more severely damaged, the underlying connective tissue will be exposed and normal serosal fibrinolytic activity will be lost[32].

Exposed endothelial and inflammatory cells, as well as damaged mesothelial cells, may produce plasminogen activator inhibitor 1 and 2, factors mediating a reduced functional fibrinolytic activity[29]. Low fibrinolytic activity allows the fibrinous adhesion to organize to a permanent fibrous adhesion[24]. Therapeutic modalities focusing on the different stages in adhesion formation include the use of anticoagulants and anti-inflammatory agents[33–35], removal of fibrinous exudates by peritoneal lavage[36], the augmentation of fibrinolysis by use of saccharose, vitamin E or recombinant tissue plasminogen activator[37], and the inhibition of fibroblast proliferation by use of steroids and 5-fluorouracil[38]. Proving clinical effectiveness remains difficult and there may be severe side-effects.

Recent animal and clinical studies evaluating mechanical separation during reperitonealization of two adjacent anatomical structures are more promising[39–42]. Non-resorbable and resorbable barriers have up to now been used mainly in experimental settings, leaving minimalization of peritoneal trauma as the main therapeutic modality in the prevention of postoperative adhesion formation.

Limitation of peritoneal injury should include attempts to reduce trauma inflicted by surgical gauze. Down *et al.*[19,20] showed in two experimental studies that the abrasive effect of gauzes causes adhesion formation. In various experimental models, used to evaluate the prevention of adhesions by different substances, peritoneal damage is created by gauze abrasion[43–47]. In 1968 Saxen and Myllarniemi[48] reviewed 309 laparotomies with adhesions present and found foreign-body granulomas in 61 per cent of cases. Remnants of gauze were the second most frequently observed foreign material (16 per cent) found in these adhesions[48].

The present study shows that peritoneal manipulation with surgical Medipres gauze after infliction of minimal peritoneal trauma produces significantly more adhesions than minimal trauma alone. The dense Zuhlke type 2–3 adhesions were thereby formed not only between traumatized lateral peritoneum and pelvic fat but also between traumatized peritoneum and the uterine horn and between uterine horn and bowel. This finding suggests that manipulation with Medipres gauze produces severe trauma of the peritoneum.

After minimal peritoneal trauma, manipulation of the peritoneum with non-surgical Fastsorb produced significantly fewer adhesions than manipulation with surgical Medipres gauze, suggesting a less traumatic influence on the peritoneum of Fastsorb textile. Indeed, there was no significant difference in the extent and type of adhesions formed after minimal peritoneal trauma alone and minimal trauma in combination with Fastsorb manipulation of the peritoneum. Thus peritoneal manipulation with non-surgical Fastsorb textile, as performed in the present study, does not seem to have a traumatizing effect on the peritoneum. Microscopic analysis of rubbed uterine horns partly confirms this conclusion: after rubbing with Medipres, severe trauma of the surfaces was seen with many infiltrating cells, whereas rubbing with Fastsorb produced little tissue damage with only a small number of infiltrating cells.

Given the fact that non-surgical Fastsorb textile meets important criteria for a gauze used for surgical purposes, and the observation that this non-abrasive textile produces fewer adhesions than the usual surgical gauzes, further study of the use of non-abrasive textile in abdominal surgery is indicated. Fastsorb textile might be a suitable substitute for Medipres gauze in surgical practice.

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Choosing the proximal anastomosis in aortobifemoral bypass

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Background The preferred method of proximal aortic anastomosis (end to end or end to side) in aortobifemoral bypass remains controversial.

Methods This is a study of 492 patients who had an aortobifemoral bypass for aortoiliac disease over 9 years in which end-to-end (166 patients) and end-to-side (326 patients) proximal aortic anastomoses were compared. The decision as to the type of anastomosis was made at operation, depending on the severity of aortic disease. Outcome was related to the site of the proximal anastomosis and the state of the distal run-off.

Results The overall perioperative mortality rate was 5 per cent. Early graft occlusion occurred in six patients in the end-to-side group and none in the end-to-end group. During follow-up nine patients (5 per cent) had graft occlusion following end-to-end anastomosis and 56 (17 per cent) following end-to-side anastomosis (cumulative patency 87 and 75 per cent respectively). Patency was not affected by the distal run-off

Discussion End-to-end anastomosis yields significantly better results than end-to-side anastomosis irrespective of distal run-off

Aortobifemoral bypass is an established treatment for aortoiliac occlusive disease[1,2]. Despite evolution in endovascular techniques this procedure still has an important role. Areas of controversy remain, however, and one relates to whether the proximal aortic anastomosis should be end to end or end to side.

The selection criteria for each anastomosis are not clearly defined and patency rates for each are seldom reported. There are no controlled trials and the significance of distal run-off has not been analysed. In this institution the decision as to which type of anastomosis to perform was made at operation depending on the severity of the arterial disease. If the aorta was relatively disease-free an end-to-side anastomosis was performed, otherwise an end-to-end anastomosis was used.

This study compared end-to-end and end-to-side proximal aortic anastomosis in relation to distal run-off with special reference to graft patency.

Patients and methods

Some 492 patients with aortoiliac disease, in the vascular service of the University of Natal Hospitals, were offered aortobifemoral reconstruction for incapacitating claudication or limb salvage between January 1985 and December 1993. They were monitored prospectively, a pro forma completed and the information stored on a computer database. These data were analysed at the end of 9 years. There were 418 men and 74 women with a mean age of 57 (range 27–89) years. A total of 255 patients (52 per cent) suffered claudication and 74 (15 per cent) had ischaemic rest pain without necrosis Necrosis involved one or more toes in 105 patients (21 per cent) and 58 (12 per cent) presented with an ischaemic ulcer on the foot or leg.

Routine preoperative investigations included segmental pressure measurement and velocity wave form analysis at the level of the common femoral artery in the groin using continuous wave Doppler ultrasonography. Aortography was performed via the retrograde femoral route or by intravenous digital subtraction angiography if the retrograde femoral route was technically difficult. Preoperative risk factors included hypertension (127 patients), ischaemic heart disease (58) and diabetes (48)

The operation was performed under thoracic epidural and general anaesthesia. A Dacron (Du Pont, Stevenage, UK) bifurcation graft was used with the proximal anastomosis placed on the juxtarenal aorta. The decision to perform an end-to-end or end-to-side anastomosis was made after examination of the aorta. The anterior part of the aorta was opened and, if it was relatively disease-free, an end-to-side anastomosis was performed If it was diseased, i.e. if it was aneurysmal, contained loose atheromatous plaque or was occluded, the aorta was transected and any debris cleared by endarterectomy or irrigation before end-to-end anastomosis. The aorta was regarded as aneurysmal when there were outpouchings of the arterial wall without necessarily an increase in aortic diameter. Distal anastomoses were routinely made to the common femoral artery bifurcations, with or without local endarterectomy. If the superficial femoral artery (SFA) was occluded, the distal anastomosis was laid over the profunda femoris artery. All patients received perioperative prophylactic antibiotics.

Following discharge from hospital all patients were given follow-up appointments in the vascular clinic at intervals of 1 month, 3 months and 6-monthly for an indefinite period.

Life-table analysis was used to calculate the 5-year patency rates. The χ^2 method was used for statistical analysis.

Results

Table 1 shows complications that occurred within 1 month of operation. The total perioperative mortality rate was 5 per cent (25 patients). Fifteen patients died from myocardial infarction, two from respiratory failure, three from renal failure and five from miscellaneous causes including pulmonary embolism, bowel infarction, stroke and aortoenteric fistula. Six deaths (4 per cent) occurred in the end-to-end anastomosis group and 19 (6 per cent) in the end-to-side group.

Graft occlusion occurred within 1 month in six patients following end-to-side anastomosis (one graft limb occluded in four and the whole graft in two patients). In three patients this was due to technical problems and the grafts were successfully reopened, while in the other three occlusion was due to poor run-off and the graft could not be salvaged. No patient developed early graft occlusion

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Table 1 Complications within 1 month of operation

	No. of patients ($n = 492$)
General	
Death*	25 (5)
Respiratory	21 (4)
Myocardial infarction	15 (3)
Intestinal obstruction	4 (1)
Deep vein thrombosis	4 (1)
Stroke	2 (1)
Other	6
Local	
Wound sepsis*	19 (4)
Abdomen	9 (2)
Groin	11 (2)
Graft occlusion	6 (1)

Values in parentheses are percentages. *For cause of death, see text; one patient had wound sepsis in both the groin and abdomen

Table 2 Late graft occlusion rates following aortobifemoral bypass

	End-to-end anastomosis ($n = 166$)	End-to-side anastomosis ($n = 326$)	P*
Single graft limb	5 (3)	46 (14)	0·0001
Whole graft	4 (2)	10 (3)	n.s.
Total	9 (5)	56 (17)	0·0001

Values in parentheses are percentages n.s., Not significant. *χ^2 test

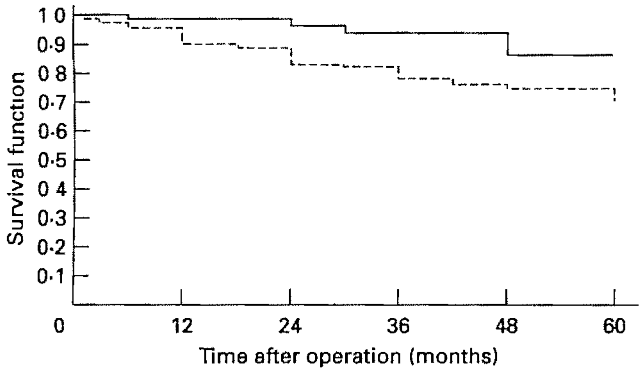

Fig. 1 Five-year patency rates in patients with end-to-end anastomosis (———) and in those with end-to-side anastomosis (– – –) as calculated by life-table analysis

following end-to-end anastomosis. During follow-up, nine patients (5 per cent) with an end-to-end anastomosis and 56 patients (17 per cent) with an end-to-side anastomosis developed graft occlusion ($P < 0·0001$). Unilateral graft limb occlusion occurred significantly more frequently in the end-to-side group (*Table 2*). Four patients (2 per cent) developed late graft sepsis after end-to-end anastomosis compared with nine (3 per cent) following end-to-side anastomosis (P not significant).

Five-year cumulative patency was 87 per cent after end-to-end anastomosis and 75 per cent after end-to-side anastomosis ($P < 0·0001$) (*Fig. 1*).

The graft occlusion rate was compared in patients with a patent or occluded SFA. Each limb was analysed separately. Of the 984 distal anastomoses, 285 graft limbs were anastomosed to a patent SFA (two vessel or common femoral run-off) in the end-to-end group and 576 in the end-to-side group. There were 47 limbs with an occluded SFA (profunda run-off) in the end-to-end group and 76 in the end-to-side group. After end-to-end anastomosis there was no difference in the rate of occlusion between graft limbs anastomosed to a patent SFA (3 per cent) and those with profunda run-off only (2 per cent). Following end-to-side anastomosis the difference in occlusion rates between graft limbs anastomosed to a patent SFA (9 per cent) and those with profunda run-off only (30 per cent) was statistically significant ($P = 0·0001$). In limbs with a patent SFA there was a significant difference in occlusion rate between end-to-end and end-to-side proximal anastomosis (3 *versus* 9 per cent; $P < 0·05$); and in limbs with profunda run-off only there was also a significant difference between end-to-end and end-to-side proximal anastomosis (2 *versus* 30 per cent; $P = 0·001$).

Discussion

Aortobifemoral bypass is an established treatment for aortoiliac occlusive disease. With the evolution of extra-anatomic bypass and endovascular techniques, however, fewer procedures of this type will be performed. The preferred method of proximal aortic anastomosis remains controversial. Some surgeons prefer end-to-end proximal anastomosis while others obtain comparable results with end-to-side proximal anastomosis[1,2]. The end-to-end anastomosis has the theoretical advantage of less turbulence at the anastomosis; furthermore, the graft does not protrude anteriorly against the duodenum and the graft limbs are less likely to kink. In addition, the distal aorta, the most common site for aneurysms and a potential source of emboli from ulcerated plaques, is excluded[2]. Theoretical advantages of an end-to-side anastomosis are that the operation is technically simpler, the inferior mesenteric artery is preserved and in case of graft occlusion there may be sufficient flow through the iliac arteries to prevent limb loss. There may be an increased risk of impotence following end-to-end anastomosis[2].

All operations in this study were performed in the same unit and important techniques were identical in the two groups. Although not randomized, the proximal anastomosis in all patients was placed in the juxtarenal segment of the aorta.

The decision to perform end-to-end or end-to-side anastomosis was governed by the appearance of the aorta at operation. Preoperative angiography played no part in this decision. Transecting the diseased aorta with an endarterectomy prevents embolization of debris. If the aorta is free from disease, then either anastomosis would suffice but an end-to-side anastomosis is quicker and easier to construct. The findings in this series argue against this protocol as patients with end-to-end proximal anastomosis did significantly better than those who had end-to-side anastomosis.

The mortality rate reported in different series ranges between 2 and 6 per cent[1,3–6]. The mortality rate of 5 per cent in this study was at the upper limit of reported values but there was no difference between the two groups.

The reported 5-year patency rate is 75–95 per cent[1,7–11] and the rates of 87 and 75 per cent in this study were comparable. The late occlusion rate following end-to-side anastomosis was significantly higher than that after end-to-end anastomosis and the overall 5-year patency rate was significantly higher in the latter group. The whole graft occlusion rate was similar in both groups but the incidence of unilateral graft limb occlusion was significantly higher following end-to-side anastomosis. Distal run-off did not influence the rate of occlusion in patients with an end-to-end anastomosis but in those with an end-to-side anastomosis there were more occlusions in patients with profunda run-off. Irrespective of run-off, there were more occlusions following end-to-side anastomosis.

Although earlier studies[12 13] reported higher patency rates for end-to-end anastomosis, others[14,15] have not found any difference. This discrepancy was possibly the result of more careful selection[15]. Gaylis[16] concluded that end-to-end anastomosis was preferable by demonstrating angulation at the origin of the limbs of the prosthesis in an end-to-side graft.

Although the present study was not randomized, end-to-end proximal aortic anastomosis yielded significantly more favourable results compared with end-to-side anastomosis. The superiority of end-to-end anastomosis was not affected by the state of the distal run-off. End-to-end proximal anastomosis should be used in aorto-bifemoral bypass.

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Effects of serotonin and endothelin on the smooth muscle cells of autogenous vein grafts

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Background The purpose of this study was to compare the effects of vasoconstrictor substances such as 5-hydroxytryptamine (5-HT) and endothelin on the smooth muscle of canine femoral veins and vein grafts.

Methods The right canine femoral vein was grafted into the right femoral artery. The left femoral vein was used as a control. In other experiments to examine the effects of surgical procedures such as dissection of the adventitia and the effects of grafting (vein-to-vein bypass), the right femoral vein was dissected out but not removed for grafting and an autogenous vein bypass of the right femoral vein was made using the left femoral vein. In all experiments, the veins were removed 4 weeks after operation and suspended in organ chambers for isometric tension recording.

Results Maximum contractions to endothelin were comparable in control vein and vein grafts. In control vein, the maximum contraction to 5-HT was small, and was inhibited by both methiothepin, a 5-HT$_1$ and 5-HT$_2$ antagonist, and sarpogrelate hydrochloride, a 5-HT$_2$ antagonist. In vein grafts 5-HT produced significantly larger contractions than in control veins, which were inhibited by methiothepin but not by the 5-HT$_2$ antagonist. In veins with adventitial dissection alone and vein-to-vein grafts, 5-HT produced small contractions which were comparable to those in control vein.

Conclusion The larger contraction response to 5-HT in canine vein grafts may be due to an increased responsiveness of the 5-HT$_1$ receptor caused by grafting into the arterial circulation.

Endothelin is an endothelium-derived peptide which induces strong and prolonged contractions in vascular smooth muscle[1]. It is also a potent coronary, renal and systemic vasoconstrictor. The relationship between endothelin and vasospasm is important in coronary or peripheral arterial reconstruction using autogenous vein grafts Miller *et al.*[2] reported that venous smooth muscle is more sensitive than arterial smooth muscle to endothelin; however, little information is available about the effects of endothelin on the smooth muscle cells of autogenous vein grafts.

5-Hydroxytryptamine (5-HT; serotonin) is an important vasospastic agent[3,4] which causes arterial spasm in several clinical conditions, and is implicated in the pathogenesis of coronary artery and vein graft spasm[5-7]. A variable response to 5-HT has been reported in experimental autogenous grafts[8-10], although the mechanism remains unknown. In this study the effect of 5-HT and endothelin on the smooth muscle of both canine femoral veins and vein grafts was investigated. In addition, the present studies were designed to examine whether the contractile response to 5-HT and endothelin was affected when run-off beyond the femoral vein grafts was poor[11].

Materials and methods

Thirty mongrel dogs (weighing 12–20 kg) of both sexes were studied Sterile conditions were maintained throughout and sodium pentobarbital (30 mg/kg) was given intravenously during the operations. Intravenous cefmetazon (Sankyo, Tokyo, Japan) (60 mg/kg) was used for perioperative antibiotic prophylaxis

All animal care complied with the Animal Welfare Act and the guidelines for the care of laboratory animals from the National Institute of Health

Experiment 1

The purpose was to compare the effects of vasoconstrictor substances (5-HT and endothelin) on the smooth muscle of the canine femoral vein (unoperated) and autogenous vein grafts under normal run-off conditions.

Surgical procedures (n = 6) All animals were anaesthetized and the right femoral artery and vein exposed. A 4-cm length of femoral vein was harvested and preserved in heparinized saline The femoral artery was resected and reconstructed with reversed femoral vein using an end-to-end anastomosis with interrupted 7–0 monofilament sutures. After 4 weeks, the graft and contralateral femoral vein were exposed and excised The left femoral vein was used as an unoperated control.

In vitro *experiment.* The excised vessels were placed in modified Krebs–Henseleit solution of the following millimolar composition: sodium chloride, 120, potassium chloride, 5·9; calcium chloride, 2·6; magnesium sulphate, 1·0; potassium hydrogen phosphate, 1·0; sodium hydrogen carbonate, 20 0; glucose, 10·0[12]. After the blood vessels had been cleaned of any connective tissue, being careful not to touch the luminal surface, rings measuring 5 mm in length were prepared In some rings the endothelium was removed by rubbing the luminal surface gently with forceps The rings were suspended for measurement of isometric contraction in an organ chamber between a chip and a force transducer (type TB-611T; Nihon Koden, Tokyo, Japan) using two stainless steel wires inserted into the lumen of the ring. The organ chamber was filled with 20 ml Krebs–Henseleit solution at 37°C and gassed with 95 per cent oxygen and 5 per cent carbon dioxide The rings were progressively stretched and contracted with a submaximal concentration of noradrenaline (3×10^{-7} mol/l) at each level of stretch until the active maximal tension was achieved (optimal length). The rings were allowed to

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equilibrate for 30 min before the application of drugs. Cumulative concentration–response curves to the agonists were obtained in the following order: 5-HT (from 10^{-9} to 3×10^{-5} mol/l) and endothelin (from 10^{-12} to 3×10^{-8} mol/l).

Experiment 2

The purpose was to compare the effects of the vasoconstrictors 5-HT and endothelin on the smooth muscle of autogenous vein grafts under conditions of normal and poor run-off.

Surgical procedures normal and poor run-off ($n = 6$). First, a canine poor run-off model was prepared in the right leg according to the method of Morinaga *et al.*[11]. All tributary arteries distal to the saphenous artery in the right posterior leg were ligated and divided, except for one superior branch of the posterior femoral artery. After 4 weeks, the haemodynamics were believed to have stabilized and the collateralization was considered complete. A right autologous vein graft implantation was then performed as described above. In addition, the left femoral vein was grafted into the left femoral artery under normal flow conditions. After a further 4 weeks, both grafts were exposed and excised.

Isometric tension studies (5-HT) were performed as described above

Experiment 3

The purpose was to examine the effects of surgical procedures on 5-HT sensitivity in smooth muscle cells.

Surgical procedures. dissected adventitia group ($n = 6$). The right femoral vein was dissected from the adventitia without grafting. After 4 weeks the vein was exposed and excised.

Surgical procedures· vein-to-vein group ($n = 6$) The right and left femoral veins were exposed. A 4-cm length of left femoral vein was harvested and preserved in heparinized saline. The right femoral vein was reconstructed using left femoral vein with an end-to-end anastomosis with interrupted 7–0 monofilament sutures. After 4 weeks the graft was exposed and excised.

Isometric tension studies (5-HT) were performed as described above.

Experiment 4

The purpose was to examine any alterations in serotonergic receptor expression in experimental vein grafts

Surgical procedures ($n = 6$) The right femoral vein was grafted into the right femoral artery as described for experiment 1. After 4 weeks the graft and contralateral femoral vein were exposed and excised. The left femoral vein was used as an unoperated control.

In vitro *experiment* Three rings taken from the graft and control vein were divided into three groups, including a no preincubation group (controls), a preincubation with methiothepin group (5-HT_1 and 5-HT_2 antagonist, 10^{-6} mol/l)[9] and a group that had preincubation with sarpogrelate hydrochloride (5-HT_2 antagonist; 10^{-6} mol/l)[13] After each ring had been incubated with each drug for 30 min, the cumulative concentration curves of 5-HT were recorded as described for experiment 1.

Drugs

The following drugs were used: 1-noradrenaline bitartrate, 5-HT (Sigma Chemical, St Louis, Missouri, USA), endothelin 1 (American Peptide Company, San Francisco, California, USA), methiothepin (Hoffman-La Roche, Nutley, New Jersey, USA) and sarpogrelate hydrochloride (Tokyo Tanabe, Tokyo, Japan). Unless otherwise specified, all drugs were prepared daily in distilled water, kept on ice and added to the organ chambers. The drug concentrations are reported as the final molar concentrations (mol/l) in the bath solution.

Calculations and statistical analysis

Results were expressed as mean(s.e.m.). Unless otherwise specified, *n* represents the number of rings taken from different dogs. For contractions evoked by 5-HT or endothelin, the effective concentration was considered to be that producing 50 per cent (EC_{50}) of the maximum contraction evoked by 5-HT 3×10^{-5} mol/l or endothelin 3×10^{-8} mol/l Statistical evaluation was done using Student's *t* test for paired observations When more than two means were compared, analysis of variance was used. If a significant value was found, Scheffe's test for multiple comparisons was used to identify differences between the groups. The values were considered statistically different when $P < 0{\cdot}05$.

Results

Experiment 1

Optimal tension was comparable in control vein and autogenous vein grafts in normal run-off conditions with and without endothelium (*Table 1*).

Endothelin produced dose-dependent and endothelium-independent contractions in both the control veins and vein grafts under conditions of normal run-off. The maximum contraction caused by the addition of endothelin 3×10^{-8} mol/l was 4·42(0·76) g in control veins and 3·95(0·67) g in vein grafts under normal run-off conditions, and no significant difference between these was observed. In addition, at an effective concentration inducing 50 per cent of the maximum contraction (EC_{50}), no significant difference was seen between the two groups (*Table 2*; *Fig. 1*).

Table 1 Optimal tension in control vein and autogenous vein grafts with and without endothelium

	Optimal tension (g)		
	Graft (normal run-off)	Graft (poor run-off)	Vein
With endothelium	1·24(0·20)	1·30(0·30)	1·27(0·10)
Without endothelium	1·12(0·17)	1·20(0·20)	1·30(0·11)

Values are mean(s.e.m.)

Table 2 Contractility to noradrenaline and endothelium in each vessel

	EC_{50} (logM)		
	Graft (normal run-off)	Graft (poor run-off)	Vein
Noradrenaline			
With endothelium	−6·83(0·13)	−6·65(0·07)	−6·55(0·10)
Without endothelium	−6·94(0·11)	−6·63(0·18)	−6·79(0·04)
Endothelin			
With endothelium	−9·40(0·11)	−9·20(0·20)	−9·55(0·18)
Without endothelium	−9·48(0·18)	−9·40(0·20)	−9·74(0·11)

Values are mean(s.e.m.). EC_{50}, effective concentration producing 50 per cent of the maximum contraction induced by noradrenaline or endothelin (3×10^{-7} mol/l)

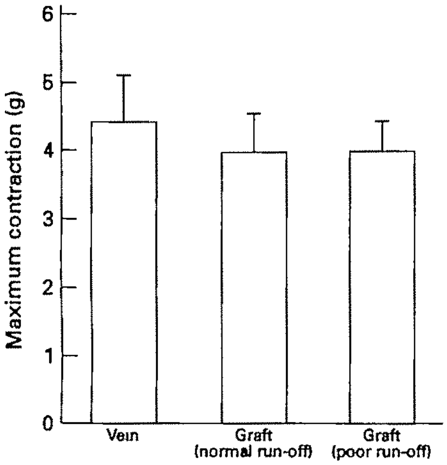

Fig. 1 Maximum contractions to endothelin (3×10^{-8} mol/l) in control femoral veins and vein grafts with normal or poor run-off. Values are mean(s.e.m.)

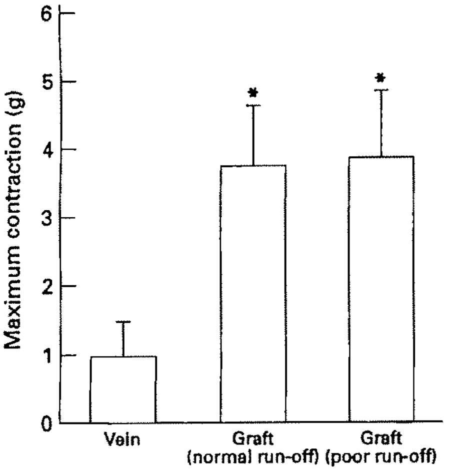

Fig. 2 Maximum contractions to serotonin (3×10^{-5} mol/l) in control femoral veins and vein grafts with normal or poor run-off Values are mean(s.e m.). $^*P < 0\cdot01$ *versus* control vein (Student's *t* test)

In the vein grafts, 5-HT produced dose-dependent and endothelium-independent contraction under conditions of normal run-off. The maximum contraction caused by the addition of 5-HT 3×10^{-5} mol/l was 3·70(0·78) g under normal run-off conditions; no significant difference was observed between the two groups. However, in control veins 5-HT produced only small contractions (0·94(0·53) g), significantly less than those of the vein grafts (*Fig. 2*).

Experiment 2

The flow rates were 70·0(18·6) ml/min in vein grafts with normal flow and 28·4(8·6) ml/min in those with poor run-off, a significant difference. Mean(s.e.m.) intimal thickening in the vein grafts was 106·8(38·2) μm in poor run-off legs *versus* 60·8(26·8) μm in control legs, again a significant difference.

Optimal tension was comparable in autogenous vein grafts under conditions of normal and poor run-off, both with and without endothelium (*Table 1*).

Endothelin produced dose-dependent and endothelium-independent contractions in vein grafts with normal and poor run-off. The maximum contraction caused by the addition of endothelin 3×10^{-8} mol/l was 3·95(0·67) g in vein grafts with normal run-off and 4·0(0·50) g in those with poor run-off. Neither was there a significant difference in EC_{50} between the two groups (*Table 2*; *Fig. 1*).

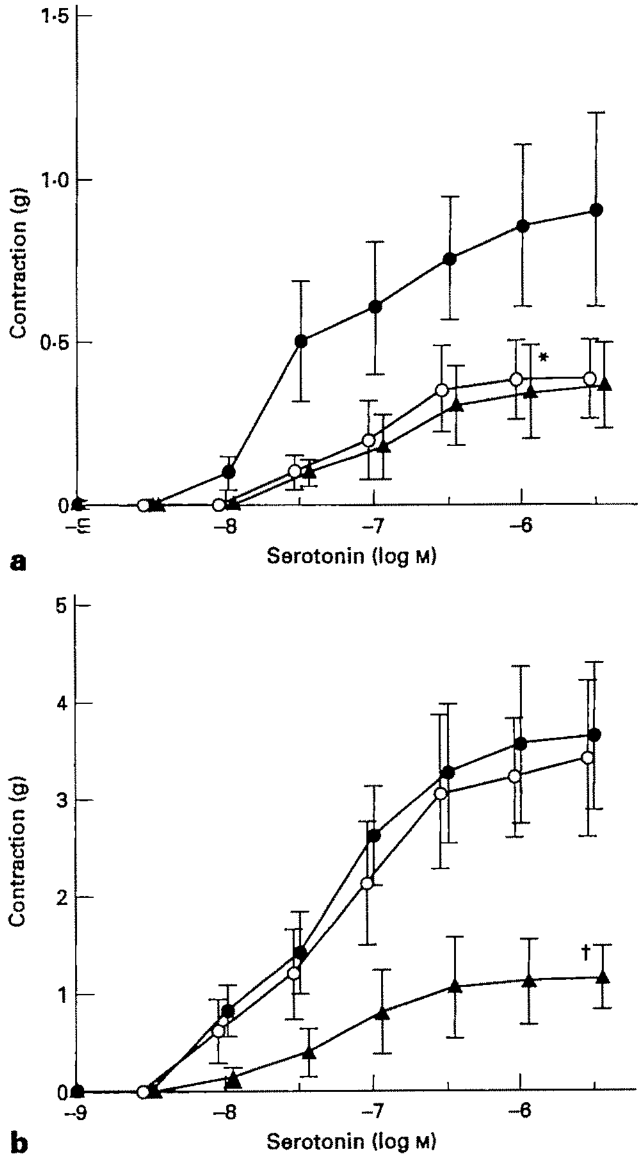

Fig. 3 Cumulative concentration–response curves to serotonin in a control veins and b vein grafts: ●, untreated; ○, sarpogrelate hydrochloride (10^{-6} mol/l); ▲, methiothepin (10^{-6} mol/l). Values are mean(s.e.m.). $^*P < 0\cdot05$ (sarpogrelate and methiothepin *versus* untreated control), $^\dagger P < 0\cdot05$ (methiothepin *versus* sarpogrelate and control) (Student's *t* test)

In vein grafts, 5-HT produced dose-dependent and endothelium-independent contractions in both normal and poor run-off conditions. The maximum contraction caused by the addition of 5-HT 3×10^{-5} mol/l was 3·70(0·78) g in vein grafts with normal run-off and 3·80(0·80) g in those with poor run-off (*Fig. 2*).

Experiment 3

Optimal tension was similar in control vein, dissected adventitia and vein-to-vein graft groups (*Table 1*).

Maximum contraction caused by the addition of 5-HT 3×10^{-5} mol/l was 0·98(0·56) g in the dissected adventitia group, 1·0(0·60) g in the vein-to-vein graft group and 0·94(0·53) g in control veins. No significant differences were observed between the three groups.

Experiment 4

Optimal tension was similar in the methiothepin, sarpogrelate hydrochloride and untreated groups (*Table 1*).

In femoral veins, 5-HT produced dose-dependent contractions (maximum 0·90(0·30) g). 5-HT-induced contractions were significantly inhibited by methiothepin (0·36(0·13) g) and sarpogrelate hydrochloride (0·38(0·12) g) (*Fig. 3*).

In the vein grafts, 5-HT produced dose-dependent contractions in the untreated group; the maximum contraction was 3·62(0·75) g. In the presence of sarpogrelate hydrochloride, the 5-HT-induced maximum contraction (3·40(0·80) g) was comparable to that of the untreated group. On the other hand, methiothepin significantly inhibited 5-HT-induced contraction (1·14(0·32) g) (*Fig. 4*).

Discussion

It has been reported that the function of vascular endothelium is altered in its capacity to release endothelium-derived relaxing factor (EDRF) when used as a vascular graft[9,12,14–17]. Impairment of the endothelium-dependent response in vein grafts may contribute to graft failure. On the other hand, the contractile response of smooth muscle cells, the other component of a vein graft, may become altered after being grafted into the arterial circulation[8–10]. In this study contractile responses of endothelin, a new agonist of endothelium-derived peptide, and serotonin (5-HT), a platelet-derived agonist, were examined.

Endothelin is a very powerful vasoconstrictor derived from the endothelium; it induces sustained contraction in various vessels[1,18,19]. The vasoconstrictive effect of endothelin on vein is stronger than on the artery of the dog[2]. The high potency of endothelin as a contractile agonist makes it useful for investigating many vasospastic diseases. It has been reported that the plasma endothelin concentration is increased in pathological states such as myocardial infarction, essential hypertension and cerebral vasospasm[20–22]. Two preliminary reports also suggested the involvement of endothelin in Raynaud's phenomenon[23,24]. In the present study endothelin produced the same strong dose-dependent contraction in both control veins and autogenous vein grafts. In addition, there was no change in the vascular sensitivity to endothelin in canine autogenous vein grafts with poor run-off.

The vasoactive effects of serotonin (5-HT), a factor released during platelet aggregation, have been evaluated extensively *in vitro* using vascular ring preparations. 5-HT may be an important mediator of coronary vasospasm in a variant of ischaemic heart disease[25]. Augmented vasoconstrictor responses to 5-HT have been reported in atherosclerotic blood vessels of animals and humans[26–28]. The present study demonstrated that in canine vein grafts 5-HT produced larger contractions than in control veins. These findings were similar to previous observations in rabbit jugular vein grafts[8–10]. Saphenous vein grafts used for aortocoronary bypass or peripheral arterial occlusive disease are subject to spasm[29–31]. The present results suggest that increased responsiveness to 5-HT may play an important role in chronic vasospasm of vein grafts. Human saphenous vein as well as canine femoral vein contracts in response to 5-HT but does not exhibit endothelium-dependent relaxation[32]. The 5-HT-induced maximum tension produced in human saphenous vein grafts is significantly less than that seen in human saphenous veins[33,34]. Thus, human vein graft data differ from those derived from experimental vein grafts. Further detailed experiments to elucidate the mechanisms contributing to chronic vasospasm of vein grafts are indicated.

5-HT is an important vasospastic agent[4,25]. Two major subclasses (5-HT_1 and 5-HT_2 receptors) have been identified with radioligand binding techniques in brain tissue specimens[35,36]. In the present study 5-HT-induced contractions in the canine femoral vein (unoperated) may have been mediated by the activation of 5-HT_2 serotonergic receptors, as they were attenuated by methiothepin, a 5-HT_1 and 5-HT_2 antagonist[9], and by sarpogrelate hydrochloride, a 5-HT_2 antagonist[13]. Alternatively, 5-HT-induced enhanced contractions in the vein grafts might be mediated by the activation of 5-HT_1 serotonergic receptors, because they were attenuated by methiothepin but not by sarpogrelate hydrochloride. The results suggest that the contractile response of canine femoral vein grafts may be caused by an increased responsiveness of 5-HT_1 receptors in smooth muscle cells. Similar conclusions have also been reached in rabbit jugular vein grafts; Komori *et al.*[9] concluded that the vasoconstrictor response in rabbit jugular vein grafts is due to an increased responsiveness of 5-HT_1 receptors. In contrast, the contraction elicited by serotonin in human and porcine coronary arteries is mediated by the activation of 5-HT_2 serotonergic receptors. Monoamine also causes the release of EDRF through the activation of endothelial 5-HT_1 receptors[25]. Thus, the pronounced contractions in canine vein grafts caused by serotonin may be due to the increased responsiveness of the 5-HT_1 receptor on the smooth muscle cell.

The present experiments also examined the effects of surgical procedures such as dissection of adventitia or vein-to-vein grafting on 5-HT sensitivity in smooth muscle cells. In veins that had adventitial dissection or vein-to-vein grafting, 5-HT produced small contractions, similar to those in control veins. These results suggest that the significant alterations in vein graft response to 5-HT may be due to changes in the properties of the vein graft smooth muscle cells caused by arterialization, not by surgical preparation.

Autologous vein is the optimum graft for surgical treatment of peripheral arterial occlusions[37–39] but late graft failure remains a significant problem, particularly in cases of poor run-off. Haemodynamic factors such as low flow velocity and low shear stress also result in late graft failure because of intimal thickening[11,40–43]. This experiment used a poor run-off model of canine autogenous vein grafts[11], a situation similar to that in patients with peripheral vascular disease. When there is poor run-off, intimal thickening of an autogenous vein graft is enhanced[11]. In the present experiment, the contractile response to serotonin and endothelin in vein grafts with poor run-off was comparable to that in those with normal flow. These results suggest that there is no difference in the function of smooth muscle cells in grafts with poor run-off despite significantly greater intimal thickening.

Endothelin produced similar contractions in both control vein and vein grafts irrespective of blood flow changes. On the other hand, 5-HT produced significantly greater contractions in vein grafts than in control veins. These findings may be the result of increased responsiveness of the 5-HT_1 receptor in smooth muscle cells of vein grafts, caused by insertion into the arterial circulation.

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Lower limb ischaemia–reperfusion injury alters gastrointestinal structure and function

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Background It has been suggested that bowel permeability is altered following abdominal aortic aneurysm surgery. The effect of ischaemia–reperfusion injury to the lower limb on the morphological structure, neutrophil infiltration and permeability of the bowel was investigated.

Methods Histological assessment of the bowel was undertaken in five groups of Wistar rats: control, 3 h of bilateral hind limb ischaemia and 3 h of bilateral hind limb ischaemia followed by 1, 2 or 3 h of reperfusion. Using an everted gut sac model and ^{14}C-labelled polyethylene glycol, the effect of ischaemia–reperfusion on small bowel permeability was studied.

Results The small bowel showed a significant decrease in mucosal thickness, villus height and crypt depth in animals subjected to ischaemia followed by 2-hr reperfusion (mean(s.e.m.) 420(15), 217(9) and 163(6) μm respectively) compared with controls (481(1[illegible]), 245(6) and 195(6) μm) ($P < 0{\cdot}05$). Neutrophil count within the lamina propria was similar in the different groups. A significant increase in mean(s.e.m.) ^{14}C-labelled polyethylene glycol translocation was detected in animals subjected to ischaemia–reperfusion compared with controls (760(40) *versus* 560(27) c.p.m. per ml per h) ($P < 0{\cdot}05$).

Conclusion These data suggest that reperfusion of acutely ischaemic extremities produces structural and functional changes in the small intestine, although these changes are not associated with increased neutrophil infiltration within the bowel wall.

The gut lumen normally contains numerous species of bacteria and has a high local concentration of endotoxins. Under normal circumstances, the intestinal mucosa functions as a local defence barrier which protects the host from intraluminal bacteria and their toxins[1]. The physical integrity of the gut mucosa represents the mainstay of the gut 'barrier', supported by various components of the host immune system including cell-mediated immunity, systemic immunity (serum immunoglobulin (Ig) G and IgM) and secretory immunity on the mucosal surface (sIgA)[2].

Alteration in intestinal permeability has been described in a variety of clinical conditions[3–5]. However, over recent years interest has focused on the role of intestinal barrier failure in the pathogenesis of sepsis and multiple organ dysfunction syndrome in relation to acute conditions such as thermal injury, trauma, major surgery and other forms of critical illness[6–8]. Accumulating clinical evidence suggests that many of the systemic complications observed in these groups of patients could be related to a systemic inflammatory response initiated by translocation of bacteria or their toxins through an altered intestinal barrier into the systemic circulation.

Recent reports suggest that bowel permeability is altered in patients following abdominal aortic aneurysm surgery[8,9]. Experimental work also suggests that lower limb ischaemia–reperfusion disrupts intestinal mucosal tight junctions, leading to endotoxaemia[10]. In both experimental animals and humans, reperfusion of the acutely ischaemic lower limb has been shown to cause pulmonary injury associated with increased microvascular permeability and polymorphonuclear neutrophil (PMN) infiltration within the lung[11,12].

The purpose of this study was to determine the effect of acute ischaemia–reperfusion of the lower limb on intestinal mucosal structure and PMN infiltration within the bowel wall and, second, to assess quantitatively the effect of this insult on the permeability of the bowel in a rat model.

Materials and methods

Animal model

Adult male Wistar rats weighing 300–310 g (obtained from a breeding colony) were used in the study. Animals were kept under standard conditions and had free access to standard rat chow (R. Morton, Ballymena, UK) and tap water until the morning of the experiment. The animals were anaesthetized with subcutaneous ketamine 80 mg kg^{-1} and xylazine 8 mg kg^{-1}. Hydration of the animals was maintained by injection of sterile 0·9 per cent sodium chloride (Antigen Pharmaceuticals, Roscrea, Ireland) 3 ml kg^{-1} h^{-1} subcutaneously. Using a heat lamp, body temperature was kept at 37°C. Bilateral hind limb ischaemia was induced by applying rubber band tourniquets high around each thigh as originally described by Rosenthal[13]. At the end of the period of ischaemia, reperfusion of the limbs was achieved by releasing the tourniquets. Animals were killed by cervical dislocation at the end of the experiment All procedures

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involving animals were carried out in accordance with the regulations of the UK Animals (Scientific Procedures) Act 1986.

Experiment 1: Histological assessment of the bowel

Light microscopic assessment of the small and large bowel was carried out in five groups of rats (12 animals in each group): group 1 (control) had 6 h of general anaesthesia only; group 2 had 3 h of bilateral hind limb ischaemia without reperfusion; groups 3, 4 and 5 had 3 h of bilateral hind limb ischaemia followed by 1, 2 or 3 h of reperfusion. In each animal at the end of the experimental period, a midline laparotomy was performed and a 5-cm long intestinal segment was obtained from the terminal ileum and proximal colon. These were opened along their length with scissors, washed with a 0·9 per cent solution of sodium chloride and immediately placed in 10 per cent formalin.

Tissue samples were fixed for at least 48 h. Tissue was embedded in paraffin wax and 5-μm sections were cut and stained with haematoxylin and eosin. Histological evaluation was performed by an independent pathologist who had no knowledge of the experimental groups from which the specimens were derived. The sections were carefully examined microscopically and well oriented areas showing good preservation of structural and cytological details were selected for morphometric assessment using the Kontron computerized Image Analysis System (Kontron Electronics, Munich, Germany). The following parameters were measured in the small bowel: total mucosal thickness, mean villus height and mean crypt depth. The large intestine was assessed by measuring total mucosal thickness and mean crypt depth. For each rat, 20 measurements of each parameter were made and the mean was calculated.

In addition, in both the small and large bowel, a marked area of lamina propria was measured (in mm^2) and the number of PMNs within this area was counted manually to assess neutrophil infiltration within the intestinal wall. This was expressed as PMNs per mm^2.

Experiment 2: Assessment of intestinal permeability

Regional characteristics of normal intestinal permeability. An initial study was undertaken to determine the regional characteristics of intestinal permeability in the normal rat ($n = 10$). Employing an 'everted gut sac' model and ^{14}C-labelled polyethylene glycol 4000 ([^{14}C]PEG 4000) (Amersham International, Amersham, UK) as a permeability probe, permeability was determined along the whole length of the small intestine. In each animal a midline laparotomy was performed and the small intestine was divided at the duodenojejunal flexure proximally and the ileocaecal valve distally. The isolated bowel was removed by stripping it from its mesentery. The intestine was then divided into sequential segments 10 cm in length, starting at the duodenojejunal junction. These were placed in a cold (4°C) 0·9 per cent solution of sodium chloride. Each intestinal segment was everted over a glass pipette (1·5 mm in diameter) and the distal end of the sac was ligated with a no. 0 linen tie (Ethicon, Edinburgh, UK). Using a 1-ml syringe and a 22-G Teflon cannula (Baxter, Dublin, Ireland), the sac was filled via the proximal end with 800 μl Krebs' bicarbonate buffer solution (Sigma, Poole, UK) containing 100 μmol l^{-1} PEG 4000 (Merck, Poole, UK). The proximal end was then ligated to give an 8-cm long gut sac. The gut sacs were placed in numbered flasks with 50 ml Krebs' bicarbonate buffer solution containing 100 μmol l^{-1} PEG 4000 and 0·8 μCi [^{14}C]PEG 4000 (0·16 μCi μmol^{-1}). Sacs were incubated for 60 min in a shaking water bath (80 oscillations per min) at 37°C with continuous oxygen flow (95 per cent oxygen, 5 per cent carbon dioxide) into the flasks.

After incubation, the sacs were blotted dry and their contents drained into plastic tubes. Samples of 500 μl were taken from each sac and also from the solution contained in the incubation flask in which the sac was immersed. These were aliquoted into separate scintillation vials (Hughes and Hughes, Somerset, UK). To each vial 2·5 ml scintillation cocktail (Aquasafe 300 Plus; Zinsser Analytic, Maidenhead, UK) was added and thoroughly mixed. Radioactivity (c.p.m.) in the sac (serosal) solution was then determined with a liquid scintillation counter (Coulter Electronics, Luton, UK). The rate of [^{14}C]PEG transport into the serosal fluid was expressed as c.p.m. per ml per h.

Effect of ischaemia and reperfusion on intestinal permeability. Using the model described above, gut permeability was studied in three groups of animals (ten in each group): (1) control (5 h of general anaesthesia only); (2) 3 h of bilateral hind limb ischaemia alone; and (3) 3 h of bilateral hind limb ischaemia followed by 2 h of reperfusion. Four consecutive ileal segments 10 cm in length (starting at the ileocaecal junction) were taken from each animal (segments 1–4 respectively). The respective ileal sacs from the control, ischaemia alone and ischaemia–reperfusion groups were incubated in separate flasks.

Statistical analysis

Results are expressed as mean(s.e.m.). Kruskal–Wallis analysis of variance was used to detect differences between groups, and statistical comparisons were made with the Mann–Whitney *U* test with a level of $P < 0·05$ taken to indicate a significant difference.

Results

Morphological and morphometric assessment of the bowel

No significant mucosal damage was detected in either the small or the large bowel in any of the groups on microscopic examination. Morphometric assessment showed significant differences between animals subjected to ischaemia–reperfusion compared with control animals (*Table 1*).

Small bowel. In the small bowel, no significant difference in the mean mucosal thickness, villus height or crypt depth was detected between the control animals and animals subjected to 3 h of ischaemia alone. There was a significant decrease in mean mucosal thickness in animals subjected to ischaemia followed by reperfusion for 2 or 3 h when compared to control animals. Mean villus height decreased significantly in animals subjected to ischaemia followed by 2 h of reperfusion, compared with findings in control animals. Mean crypt depth decreased significantly in animals subjected to ischaemia followed by 2 or 3 h of reperfusion, compared with the depth in controls.

Table 1 Morphometric assessment of the small bowel

	Control ($n = 12$)	3-h ischaemia ($n = 12$)	3-h ischaemia plus 1-h reperfusion ($n = 12$)	3-h ischaemia plus 2-h reperfusion ($n = 12$)	3-h ischaemia plus 3-h reperfusion ($n = 12$)
Mucosal thickness (μm)	481(11)	460(11)	451(11)	420(15)*	420(15)*
Villus height (μm)	245(6)	240(8)	236(7)	217(9)*	225(8)
Crypt depth (μm)	195(6)	185(7)	198(8)	163(6)†	160(6)‡

Values are mean(s.e.m.). *$P < 0·05$, †$P < 0·005$, ‡$P < 0·0005$ *versus* control and ischaemia alone (Mann–Whitney *U* test)

Large bowel. In the large bowel, no significant difference was detected in mean mucosal thickness or mean crypt depth in any of the study groups when compared with findings in control animals ($P = 0{\cdot}12$ and $P = 0{\cdot}34$ respectively).

Polymorphonuclear leucocyte count In control animals the mean(s.e.m.) PMN count within the lamina propria was 37·6(1·7) PMNs per mm^2 in the small bowel and 110(20) PMNs per mm^2 in the large bowel. No significant difference in PMN count was detected when the control group was compared with any of the experimental groups in both the small ($P = 0{\cdot}50$) and large ($P = 0{\cdot}93$) bowel.

Regional characteristics of normal intestinal permeability

In normal rats, no significant regional variation in the rate of [^{14}C]PEG 4000 translocation was detected along the entire length of the small bowel ($P = 0{\cdot}90$) (*Fig. 1*).

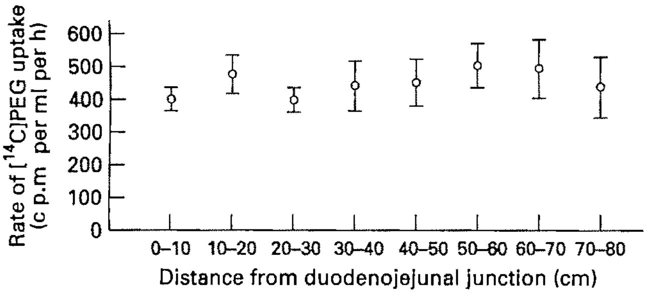

Fig. 1 Regional permeability to ^{14}C-labelled polyethylene glycol ([^{14}C]PEG) along the whole length of the small bowel (duodenojejunal flexure to terminal ileum) in ten normal rats. Values are the mean(s.e.m.) [^{14}C]PEG uptake at different distances from the duodenojejunal junction. No significant difference was detected between the different regions ($P = 0{\cdot}90$, analysis of variance)

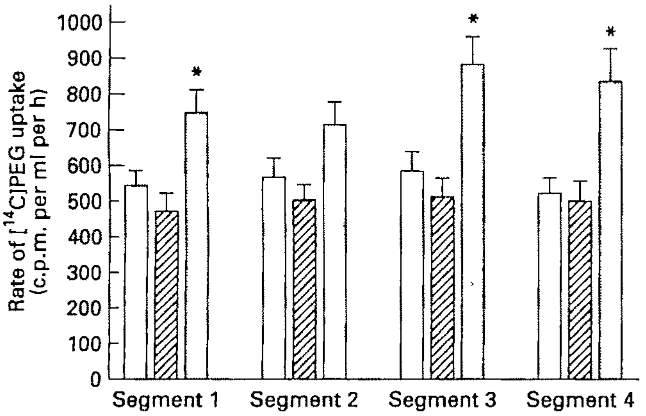

Fig. 2 Comparison of regional intestinal permeability (^{14}C-labelled polyethylene glycol ([^{14}C]PEG) uptake) between the respective intestinal segments from control animals (□, $n = 10$), rats subjected to 3-h ischaemia alone (▨, $n = 10$) and rats subjected to ischaemia followed by 2 h of reperfusion (□, $n = 10$). Four consecutive ileal segments, starting at the ileocaecal junction, were studied in each animal (segments 1–4). *$P < 0{\cdot}05$ *versus* control and ischaemia alone (Mann–Whitney *U* test)

Effect of ischaemia and reperfusion on intestinal permeability

Three hours of ischaemia alone did not significantly alter the mean(s.e.m.) rate of [^{14}C]PEG 4000 translocation (502(29) c.p.m. per ml per h) compared with that in controls (560(27) c.p.m. per ml per h) ($P = 0{\cdot}17$). However, 3 h of ischaemia followed by 2 h of reperfusion caused a significant increase in [^{14}C]PEG 4000 translocation into the intestinal sacs compared with that in controls or with ischaemia alone (760(40) c.p.m. per ml per h) ($P < 0{\cdot}05$). The increase in intestinal permeability in the reperfused animals affected all intestinal segments when compared with the respective segments from control animals (*Fig. 2*).

Discussion

A variety of histological grading and scoring systems has been used to evaluate intestinal mucosal injury[14–16]. In this study a morphometric method of assessment was employed in which measurements of the various components of intestinal mucosa were used to compare intestinal samples from the different groups. This objective and quantitative method has recently been shown to correlate strongly with histological evidence of mucosal damage[11]. More importantly, in this study, the detection of morphometric mucosal changes in the absence of demonstrable morphological changes on light microscopy carries the implication that morphometry has a higher sensitivity than morphological assessment.

The reduction of mucosal thickness observed in this study largely reflected a significant decrease in crypt depth, but the villi were affected to a lesser extent. These findings differ from the well studied local bowel ischaemia–reperfusion model in which injury characteristically starts at the tip of the villus and extends towards the base with no or minimal involvement of the crypts[16,17]. In contrast, these findings suggest that the mechanism involved in gut injury following lower limb ischaemia–reperfusion principally affects the more active crypt cells. Unlike the large bowel, the structure of the small bowel was affected by and vulnerable to lower limb ischaemia–reperfusion.

The isolated everted intestinal sac is recognized as an excellent and reliable model for studying the transfer of substances across intestinal mucosa[18–20]. It has been used to determine the absorption of a wide spectrum of nutrients (e.g. sugars, vitamins, electrolytes, minerals, albumin, and macromolecules such as horseradish peroxidase and endotoxin). The advantages of this technique are that measurements are made over a defined length and location of intestine, and under controlled conditions over a specific period of time. The model also allows analysis of intestinal permeability in the absence of the influence of *in vivo* factors.

The data obtained from the study of regional gut permeability in normal rat intestine support previous reports that there is no significant variation in permeability to PEG in different regions of the healthy small intestine[20]. The permeability characteristics of normal human intestine decrease from proximal to distal small bowel[21]. The alteration in bowel permeability observed following lower limb ischaemia–reperfusion supports the hypothesis that isolated injury to an organ remote from the gut can alter intestinal permeability[18]. In a recent study[9], the authors' group was able to demonstrate variable concentrations of endotoxin in the plasma of patients undergoing abdominal aortic aneurysm surgery. Roumen *et al.*[8] reported an increase in bowel permeability following abdominal aortic aneurysm surgery. However, the fact that there were inherent differences between patients and the control group makes it difficult to attribute the alteration in gut permeability to lower limb ischaemia–reperfusion *per se*. Factors such as the effect of general anaesthesia, the period of fasting before permeability assessment, the age and the critical state of the patients may have contributed to the alteration in bowel permeability.

The exact mechanism whereby ischaemia–reperfusion of a distant organ can alter gut permeability is not totally clear. It has been suggested that the generation of oxygen-derived free radicals via the xanthine oxidase pathway produces both local limb injury and remote lung injury following lower limb ischaemia–reperfusion[22,23]. It is possible that the difference in susceptibility to ischaemia–reperfusion injury between the small and large bowel is related to differences in their xanthine oxidase concentrations, as the small bowel has substantially higher concentrations of xanthine oxidase than the large bowel[24].

The concept of neutrophil activation by oxygen-derived free radicals remains a favoured mechanism for many investigators in explaining the local ischaemia–reperfusion injury in various organs[11,25,26]. In the present study, histological assessment of the bowel did not reveal a significant increase in the number of PMNs infiltrating the bowel mucosa, which implies that the mucosal injury was not caused by neutrophils. It could be argued that other methods such as the myeloperoxidase assay might have detected small differences in neutrophil influx. Further studies using antineutrophil adhesion antibody may help to confirm whether the alteration in gut permeability is neutrophil independent. Conflicting results have been obtained when studying ischaemia–reperfusion injury in animals depleted of PMNs. Some studies have reported that such depletion protects animals against reperfusion injury, whereas others have not[11,27,28]. It is conceivable that mediators generated in the reperfused limb, such as oxygen free radicals and thromboxane A_2, may mediate gut injury by the activation of mucosal mast cells[12,29,30].

In conclusion, this study has demonstrated qualitatively and quantitatively that reperfusion of the acutely ischaemic lower limb *per se* alters intestinal structure and permeability. This may explain the endotoxaemia reported in patients undergoing abdominal aortic aneurysm surgery, and may be related to the development of systemic complications and multiple organ dysfunction syndrome in these patients.

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Laparoscopy for the impalpable testis

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Background Use of laparoscopy in the management of the impalpable testis remains controversial. Localization of the testis may help plan or obviate the need for groin exploration. This study reviews the need for inguinal exploration with respect to laparoscopic findings, particularly of vas and vessels entering a closed deep inguinal ring.

Method Case notes of boys undergoing laparoscopy for undescended testes were reviewed retrospectively.

Results Of 86 impalpable testes, 32 were intra-abdominal and ten were absent with intra-abdominal blind ending vas and vessels. In 17 instances the vas and vessels entered an open internal ring and in 26 a closed internal ring. In one boy neither vas, vessels nor testis were visualized. Of the 26 impalpable testes with a closed internal ring, excision of testicular remnants in 18 revealed no histological testicular parenchyma, one boy had bilateral perineal ectopic testes missed clinically and six were not explored.

Conclusion The laparoscopic finding of vas and vessels entering a closed deep inguinal ring should prompt a careful examination for an ectopic testis. If a palpable testis can be ruled out, inguinal exploration is not necessary, as viable testicular parenchyma is rarely found. Laparoscopy would have avoided negative exploration in 42 per cent of impalpable testes in this series.

Laparoscopy is commonly used in the management of patients with an impalpable testis for localization and to help plan subsequent surgical management[1–3]. For example, the presence of an intra-abdominal testis may necessitate a Fowler Stephens procedure or microvascular transfer. A blind ending intra-abdominal vas and vessels requires no further surgical exploration. The presence of vas and vessels entering an open internal ring would suggest the presence of a testis and the need for exploration. Groin exploration based on the findings of vas and vessels entering a closed internal ring, however, remains controversial. Weiss and Seashore[1] reported that if a hernia was identified during laparoscopy a testis was always present on that side, whereas if a closed ring was identified the testis was absent. Presence of a closed internal ring would imply a vascular accident such as torsion following testicular descent, with residual testicular tissue infrequently present. Elder[4] advocates excision of the testicular nubbins through a low inguinal incision when vas and vessels are seen to enter a closed internal ring. This view is shared by Plotzker *et al.*[5]. This study reviewed the place of laparoscopy for impalpable testis and the need for groin exploration on the findings of vas and vessels entering a closed internal ring, correlating the results with histological examination.

Materials and methods

Patients undergoing laparoscopy for undescended testes between January 1985 and December 1995 were identified from theatre registers. Case notes were reviewed for details of age, side of undescended testis, clinical and laparoscopic findings, details of subsequent exploration if any and histology of any resected specimens. All patients were examined under a general anaesthetic with muscle relaxation. On the affected side the scrotum was palpated for the testis or gubernacular structures. If the testis remained impalpable an effort was made to 'milk' the testis down from the inguinal canal with one hand while the other blocked retraction. If no testis was palpable laparoscopy was performed by the closed method. A Veress needle was inserted through the right lower quadrant of the abdomen and a carbon dioxide pneumoperitoneum was produced. A 5-mm Storz paediatric laparoscope (Karl Storz, Tuttlingen, Germany) was then inserted through a small subumbilical incision. A closed ring was identified by the absence of a patent processus vaginalis and a perfectly flat peritoneal layer at the point where the vas and vessels entered the inguinal canal Presence of an obviously patent processus vaginalis or a crescentic fold of peritoneum at the site of the deep ring was considered an indication for groin exploration.

Results

Sixty-eight boys, aged from 6 months to 15 years (median 29 months), were identified with 86 impalpable testes. Laparoscopy was performed without complications in all patients. A summary of the results is given in *Table 1* and surgical management in *Table 2*. Thirty-two testes were found to be intra-abdominal, of which 25 underwent standard orchidopexy, four a one-stage Fowler Stephens

Table 1 Clinical and laparoscopic findings in 68 cryptorchid boys (86 impalpable testes)

	Right	Left
Intra-abdominal*	11	21
Blind ending vas	1	9
Absent vas, vessels and testis	0	1
Vas and vessels entering open ring	7	10
Vas and vessels entering closed ring	8	18
Total†	27	59

*Nine bilateral; †eighteen bilateral

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Table 2 Surgical procedures for 85 impalpable testes

	Blind ending vas and vessels	Intra-abdominal testis	Vas and vessels entering open ring	Vas and vessels entering closed ring
Orchidopexy		25	17	
One-stage Fowler Stephens		4		
Two-stage Fowler Stephens		2		
Orchidectomy		1		
Orchidopexy of ectopic testis				2
Excision of testicular remnant				18
Not explored	10			6
Total	10	32	17	26

In one boy neither vas and vessels nor testis were seen

orchidopexy, two a two-stage Fowler Stephens orchidopexy and one an orchidectomy. Ten had blind ending intra-abdominal vas and vessels and were not explored. Seventeen had vas and vessels entering an open ring and all underwent exploration and orchidopexy. Twenty-six had vas and vessels entering a closed ring of which 20 were explored; in 18 testicular remnants were excised, histology of which revealed no viable testicular parenchyma nor epididymal remnants, and two perineal ectopic testes in the same child which were missed clinically underwent orchidopexy. The remaining six patients in this group underwent careful but negative clinical examination for ectopic testes and were not explored. In one patient neither the testis, vas nor vessels were visualized. He will be reviewed before puberty.

Discussion

Testicular descent occurs through several stages. Following differentiation of the primitive gonad into the testis, it descends to the internal ring by the third month of intrauterine development. The processus vaginalis forms in the third month of gestation and extends into the scrotum. This is usually obliterated before birth or in the first year of life, after descent of the testis. Incomplete descent of the testis therefore is usually associated with a patent processus vaginalis and, conversely, closure of the processus vaginalis indicates that complete descent has occurred although the testis may lie in an ectopic position. Elder showed that 83 per cent of palpable undescended testes[6] and 97 per cent of intra-abdominal testes[4] were associated with a patent processus vaginalis.

A testis may be impalpable for various reasons. The testis may be intra-abdominal, canalicular, atrophic, dysgenetic or absent. A 'vanishing' testis is thought to be due to a vascular accident in the perinatal period[3]. Intra-abdominal blind ending vas and vessels suggest a vascular accident to an intra-abdominal testis prior to its transcanalicular migration. These are commonly not explored. Similarly, testicular absence with vas and vessels entering a closed ring represents a vascular accident following descent of the testis with residual viable testicular tissue rarely if ever present. The presence of haemosiderin or calcium deposits on histological examination supports this theory. Since the mechanism for the 'vanishing' testis is the same in both instances, the need for surgical exploration in this group should be questioned. In this series, none of the excised specimens revealed viable testicular parenchyma, in keeping with other series. Weiss and Seashore[1], in a review of 32 patients and 33 nonpalpable testes found all 12 undescended testes had an associated hernial sac whereas all 21 absent or vanishing testes had a closed processus vaginalis. Complete absence of viable testicular tissue was noted in specimens excised from all 21 patients undergoing inguinal exploration. In the authors' practice, the groin is no longer explored routinely when vas and vessels are noted to enter a closed internal ring at laparoscopy. A careful examination is made for an ectopic testis. Taking patients with blind ending vas and vessels together with vas and vessels entering a closed ring, laparoscopy would then have avoided negative exploration in 36 of 86 testes (42 per cent).

At this institute 150–180 orchidopexies are performed each year. This study of 68 boys with 86 impalpable testes represents about 5 per cent of undescended testes operated on during a 10-year period. Impalpable testes have been reported to comprise 13–41 per cent of the total population of undescended testes[7]. The lower rate in this study may result from the rigorous criteria employed to define an 'impalpable testis' including a thorough clinical examination under an anaesthetic by an experienced clinician before laparoscopy.

Laparoscopy has been widely adopted in specialist centres, has a high diagnostic yield and is safe as confirmed by several studies[1–3]. Many continue to regard surgical exploration as the definitive investigation. This approach may only be justified if a testis or vas and vessels are found, and failure to locate the testis or vas and vessels raises a diagnostic problem. In a series of 22 impalpable testes in 18 boys, Lakhoo *et al.*[8] demonstrated 13 of 22 to be present at laparoscopy. All had previously undergone a negative inguinal exploration elsewhere. In a series of 126 patients Perovic and Janic[9] demonstrated six testes to be present laparoscopically in 12 patients who had had previous exploration. Similarly of 53 impalpable testes, Boddy *et al.*[10] accounted for ten by laparoscopy, even though 13 of the boys had had a previous negative groin exploration. Inguinal exploration alone is inadequate, unjustified, unnecessarily invasive and unreliable. It is therefore appropriate that where facilities for diagnostic laparoscopy are unavailable locally, such patients should be referred to a unit offering this service[8].

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Short note

Detection of occult nodal metastases in patients with colorectal cancer

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The detection of lymph node metastasis by conventional histological techniques may fail to detect micrometastases. The magnetic activated cell sorter (MACS)[1] is superior to current cytological techniques in detecting tumour cells in the blood[2] and peritoneal cavity[3] of patients with colorectal cancer. This study determined whether the MACS could detect metastases within regional lymph nodes.

Patients and methods

Nineteen patients who had colorectal cancer surgery were selected because they had easily dissectable lymph nodes in the resected specimen. Patients who had bowel resection for benign disease acted as controls: ulcerative colitis (two patients), Crohn's disease (one) and diverticular disease (one). The harvested lymph nodes were divided into two equal portions for conventional histology and MACS separation.

Magnetic cell separation

A cellular suspension was obtained and stained as described previously[2,3]. All slides were examined by an experienced histopathologist without knowledge of the clinical details.

Results

Forty-six lymph nodes (mean of two lymph nodes per patient) were studied. Eleven patients with nodal metastases detected by conventional histological methods were also positive on MACS separation. However, in two patients in whom conventional staining failed to detect any tumour cells in the regional nodes, MACS isolated a small cluster of tumour cells suggesting the presence of occult nodal metastases (*Fig. 1*).

No positive cytology was seen in patients with benign disease, indicating that there was no cross-reactivity of monoclonal antibodies with lymphocytes and macrophages.

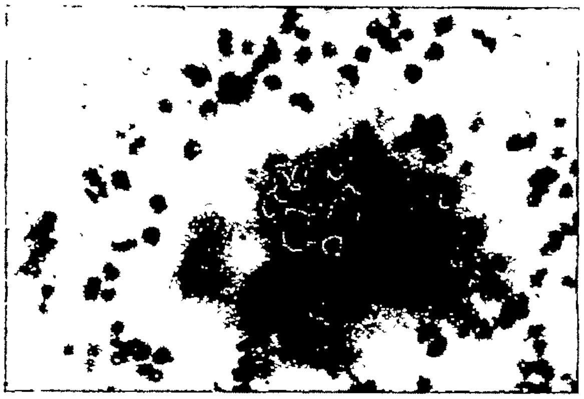

Fig. 1 The magnetic activated cell sorter isolated a cluster of tumour cells from four lymph nodes in a patient with reported Dukes' B colonic cancer

Discussion

This technique is capable of detecting occult nodal metastases that would otherwise go undetected by conventional histological examination. The significantly higher rate of detection by the MACS may occur because the whole lymph node is analysed. Conventional histology based on examination of one slide of a single section of lymph node may result in some metastases being missed.

Although excellent separation of tumour cells can be achieved with the MACS, it is far more expensive and labour intensive than conventional histological methods. The clinical significance of micrometastases in regional lymph nodes detected by means of the MACS and potential applications of this technique merit further investigation.

Acknowledgements

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Retroperitoneoscopy for the diagnosis of infiltrating retroperitoneal lymphadenopathy and masses

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Background Retroperitoneoscopy (RPS) is a form of direct vision endoscopy, used to explore the retroperitoneal space, and was first described by Bartel in 1969.

Methods RPS was performed prospectively to diagnose infiltrating retroperitoneal lymphadenopathy or masses when needle aspiration biopsy under computed tomographic guidance (NABCT) failed to establish a definite diagnosis.

Results From May 1985 to August 1995, RPS was performed in 118 patients (121 procedures). Mean hospital stay was 2·4 (range 2–5) days. The peroperative and perioperative morbidity rate was 6·6 per cent of the procedures. A precise diagnosis was obtained in 108 of the 118 patients. The sensitivity was 84 per cent for malignant lymphoma, 94 per cent for Hodgkin's lymphoma, 95 per cent for metastatic lymph nodes of carcinomas and 100 per cent for primary retroperitoneal tumours. The overall sensitivity was 91·5 per cent.

Conclusion RPS is an alternative procedure to NABCT when aspiration biopsy is not technically feasible because a lesion is too small to sample or failed to establish a precise histopathological diagnosis.

Surgical exploration of the retroperitoneal space through a direct vision endoscope without gas insufflation is called retroperitoneoscopy (RPS) and was first described by Bartel in 1969[1]. Since that first report, few studies of RPS have been published. The most important improvement to the original technique was introduced in 1980 by Hald and Rasmussen[2] who lengthened the 17-cm Maassen's mediastinoscope to a 19-cm endoscope, so that complete examination of the retroperitoneal area, located between the kidney hilum and the iliac bifurcation, could be performed in most cases from a lumbar incision. Exploration of the area, containing the obturator fossa, iliac bifurcation and aortic bifurcation, can be performed in most cases from an inguinal incision. Needle aspiration biopsy under computed tomographic guidance (NABCT) is a relatively non-invasive method for obtaining cytological material. However, the great variety of lesions arising in retroperitoneal locations[3–9], and the lack of differentiation of some of these malignancies, make it sometimes difficult to assess a precise histopathological type.

Retroperitoneoscopy has been used in the authors' institution since 1985[10] to diagnose infiltrating retroperitoneal lesions of undetermined aetiology when NABCT was not feasible or failed to establish a definite diagnosis, and to diagnose residual or recurrent retroperitoneal lymphadenopathy and masses after treatment of primary tumours or malignant lymphomas. The authors' 10-year experience with RPS in 118 patients is reported and the results compared with those of NABCT for the same indications.

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Patients and methods

Patients

From May 1985 to August 1995, 118 patients were studied prospectively; there were 73 men and 45 women with a mean age of 56 (range 15–81) years.

Indications for RPS were: retroperitoneal lesions of undetermined aetiology when NABCT could not be performed technically because their diameter was smaller than or equal to 2 cm ($n = 44$); retroperitoneal lesions of undetermined aetiology with a diameter greater than 2 cm, when NABCT failed to establish a definite histopathological diagnosis ($n = 60$); and retroperitoneal residual or recurrent lymphadenopathy or masses after treatment of primary tumours or malignant lymphomas, to diagnose complications or disease relapse when NABCT failed to establish a definite histopathological diagnosis ($n = 14$).

Clinical diagnoses suspected before RPS included Hodgkin's and non-Hodgkin's lymphoma ($n = 92$), including 30 lesions with a diameter smaller than or equal to 2 cm and 62 failures of NABCT to establish a definite histopathological diagnosis; metastatic lymph nodes of known or unknown carcinomas ($n = 18$), including 14 lesions with a diameter smaller than 2 cm and four failures of NABCT to establish a definite histopathological diagnosis; and retroperitoneal fibrosis ($n = 1$), primitive retroperitoneal tumours ($n = 3$), tuberculosis ($n = 2$), adrenal gland primary tumour ($n = 1$) and sequelae of pancreatitis ($n = 1$), all of which NABCT failed to diagnose.

Instruments

The Hald and Rasmussen endoscope is a 19-cm long direct vision light transmission tube (1072 D; Karl Storz, Tuttlingen, Germany) linked to a cold light cable. It is 1·4 cm wide at its tip and 2 cm wide at its base. A side hole facilitates the manipulation of instruments, which are introduced directly into the tube. The following endoscopic instruments are used: coagulating suction dissector (10970 EN; Karl Storz), scissors, clips forceps, biopsy forceps and puncture equipment (10970 P; Karl Storz)

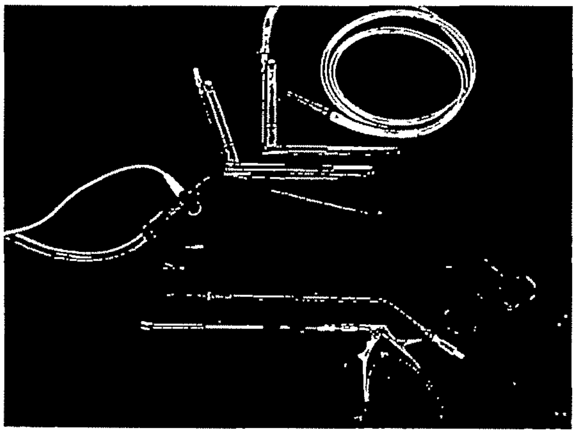

Fig. 1 Endoscopic instruments used to perform retroperitoneoscopy

(*Fig 1*). A long and narrow abdominal valve is used to retract the peritoneal contents. No gas insufflation or balloon dissector is necessary.

Procedure

Depending on the retroperitoneal area to be explored, there are two different approaches: lumboscopy enables exploration of the lumbar retroperitoneal area located between the kidney hilum and the iliac bifurcation, and extraperitoneal pelvioscopy (EPP) allows exploration of the pelvic retroperitoneal area.

Lumboscopy The patient is placed in the lumbotomy position under general anaesthesia A 3–4-cm incision is made 3 cm under the 12th rib and 3–4 cm above the anterosuperior iliac spine Cutaneous and subcutaneous incision is followed by latissimus dorsi, external oblique muscle and internal oblique muscle separation and transversus abdominis fascia incision Finger dissection identifies the retroperitoneal space and the abdominal valve is introduced to retract the peritoneal contents. The endoscope is introduced and advanced to the lumboaortic area (*Fig 2*). Structures to be sampled are progressively individualized with the coagulating suction dissector. A puncture is made to confirm the absence of vascular elements beyond the sampling area. Samples are then obtained with the biopsy forceps. Haemostasis is achieved with the coagulating suction dissector and haemostatic mesh. Suction drainage is left for 24 h in the area sampled.

Extraperitoneal pelvioscopy. Under general or spinal anaesthesia, the patient is placed in the dorsal supine position with thighs hyperextended. A 3–4-cm incision is made halfway between the anterosuperior iliac spine and the pubic spine, 3 cm above and medial to the inguinal ligament. The external oblique muscle aponeurosis is incised and muscle fibres are divided to reach the peritoneum. Finger dissection separates the peritoneum from the pelvic wall and comes in contact with the external iliac vessels. The peritoneal content is then retracted with the valve and the endoscope is introduced slightly. The external iliac artery and vein are identified From this incision, exploration can be performed from the common iliac bifurcation to the obturator fossa. Lymph nodes or lesions are dissected and sampled as described previously for lumboscopy A suction drain is left for 24 h in the area sampled.

Lumboscopy and EPP can be performed either on the left or the right side. During right lumboscopy, particular care must be taken to avoid injury to the lumbar veins.

Definitive pathological studies were requested without frozen-section examination. The location, number and characteristics of the samples were recorded after each examination.

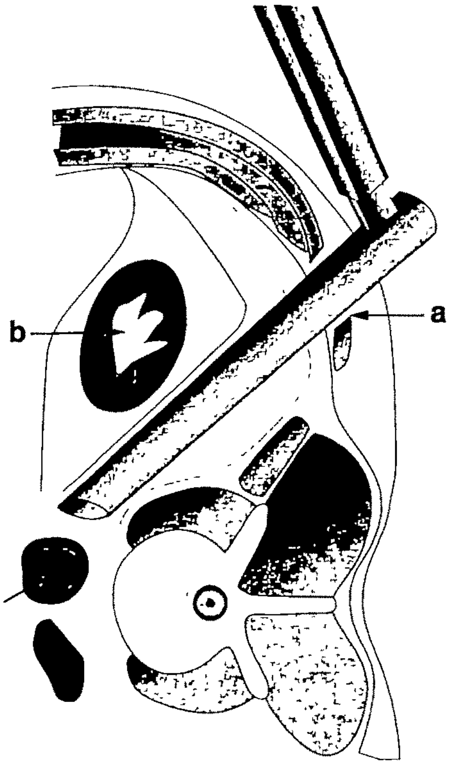

Fig. 2 Technique of lumboscopy; the endoscope is introduced through an a left lumbar incision and progresses, under b the kidney, to c the aorta

Follow-up

Follow-up was undertaken by clinical examination and abdominal CT every 3 months in order to compare RPS diagnosis with patient outcome Results were classified as positive when a precise histopathological diagnosis was obtained and therefore resulted in the appropriate treatment Results were classified as false negative when, after complete RPS, a precise histopathological diagnosis was not obtained, or when samples could not be obtained because of technical failure. The sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Results

Some 121 RPS procedures were performed (three patients had two successive examinations) comprising 92 lumboscopies (69 left and 23 right) and 29 EPPs (20 left and nine right). The mean number of samples taken during an unilateral exploration was eight (range four to 17). The mean duration of an unilateral exploration was 40 (range 20–70) min. Mean hospital stay was 2·4 (range 2–5) days. There were no intraoperative deaths and one postoperative death. The latter had no direct relation to the lumboscopy, which was performed at the terminal phase of a malignant lymphoma.

The overall morbidity rate was 6·6 per cent of the procedures (eight patients). Intraoperative complications (2·5 per cent) included one right lumbar vein injury treated by endoscopic mesh compression; one endoscopically uncontrollable haemorrhage from a partially resected large lumbar lymphadenopathy which required a lumbotomy to achieve haemostasis; and one left duplicated ureter injury which was sutured endoscopically followed by percutaneous ultrasonographically-guided pyelostomy (*Fig. 3*). Postoperative morbidity (4·1 per cent) included lymphorrhoea persisting more than 5 days in five patients which dried up spontaneously in all cases.

A definitive histopathological diagnosis was obtained in 108 of 118 patients with an overall sensitivity of 91·5 per cent. The overall specificity and overall positive predictive value were 100 per cent. The negative predictive value was 97 per cent. The precise histopathological diagnosis and the false-negative results are described in *Table 1*

In 34 patients (28·8 per cent), the clinical diagnosis suspected before RPS was radically changed by RPS data. These included 30 patients suspected to have Hodgkin's or non-Hodgkin's lymphoma (RPS diagnosis: metastatic carcinoma ($n = 13$), non-specific inflammatory lymph nodes ($n = 11$), tuberculosis ($n = 2$), sarcoidosis ($n = 2$), retroperitoneal fibrosis ($n = 1$) and sequelae of pancreatitis ($n = 1$)), three patients suspected to have a metastatic lymph node of known or unknown carcinoma (RPS diagnosis: inflammatory lymph nodes ($n = 2$) and lymphoma ($n = 1$)), and one patient suspected to have a primary adrenal gland tumour (RPS diagnosis: vena cava leiomyosarcoma).

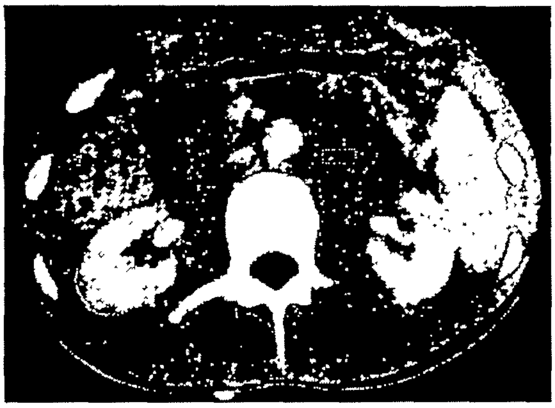

Fig. 3 Abdominal computed tomography of a 15-year-old boy with a germ cell tumour. The duplicated left ureter, surrounded by tumour infiltration (1), was injured during retroperitoneoscopy and sutured endoscopically

Table 1 Definitive pathological diagnosis, false-negative results and sensitivity of retroperitoneoscopy performed in 118 patients

	Precise pathological diagnosis by RPS	False-negative results	Sensitivity of RPS
Malignant lymphoma ($n = 52$)	44	8	0·84
Hodgkin's lymphoma ($n = 18$)	17	1	0·94
Metastatic lymph nodes of carcinomas ($n = 20$)	19	1	0·95
Primitive retroperitoneal tumours ($n = 6$)	6	0	1·00
Tuberculosis ($n = 3$)	3	0	1·00
Sarcoidosis ($n = 2$)	2	0	1·00
Non-specific inflammatory lymph nodes ($n = 13$)	13	0	1·00
Retroperitoneal fibrosis ($n = 2$)	2	0	1·00
Sequelae of acute pancreatitis ($n = 2$)	2	0	1·00

RPS, retroperitoneoscopy

Moreover, in 108 of 118 patients, the definitive diagnosis performed by RPS made it possible to change or to continue an adapted treatment. In these cases, no other procedure (except lumbotomy) could have made a precise histopathological diagnosis because there were 44 lesions smaller than 2 cm and 74 failures of NABCT.

Non-specific inflammatory lymph nodes (including chronic lymphadenitis, follicular hyperplasia, presence of macrophages in the sinuses and fibrosis) were diagnosed by RPS in 13 patients, eight of whom suffered from pyrexia of unknown origin or idiopathic inflammatory syndromes with retroperitoneal lymphadenopathy and so were suspected to have malignant lymphoma, and three of whom were suspected to have recurrence of malignant lymphoma The two remaining patients were suspected to have recurrence of retroperitoneal cancer (colonic cancer, $n = 1$; melanoma, $n = 1$). In all these patients, midterm and long-term follow-up confirmed the benign nature of the retroperitoneal adenopathy.

There were ten false-negative results Four were due to the endoscope being too short to reach the sampling area in obese patients (120–140 kg) and in four patients, who had non-Hodgkin's lymphoma, there were insufficient samples for histopathological diagnosis and immunophenotyping. The two remaining false negatives were attributable to inappropriate indications of RPS for root of mesentery infiltrations wrongly diagnosed as lymphomatous retroperitoneal lymphadenopathy by the preoperative abdominal CT.

Discussion

Benign or encapsulated retroperitoneal tumours are usually resected without preoperative pathological diagnosis. Accordingly, this study was initiated for the precise characterization of infiltrating retroperitoneal lesions. These are mostly Hodgkin's or non-Hodgkin's lymphomas, lymph node metastasis of known or unknown carcinomas, germ cell tumours or primary retroperitoneal lesions.

In most cases, the histological categorization of lymphomas requires complementary procedures to define immunological and genetic features important for differential diagnosis. These methods require several, large and adequate samples. Accordingly fresh tissue must be available for genetic analysis, and frozen and fixed tissue for immunohistochemistry and genotypic analysis.

Recently, several studies have shown that non-Hodgkin's lymphoma can be diagnosed with NABCT[11–19]. In fact, accuracies from 60 to 90 per cent have been reported but immunohistological type could be determined in no more than 40 per cent of cases. Even if a diagnosis of non-Hodgkin's lymphoma can be achieved with NABCT, many investigators maintain that large histological sections are often necessary to classify the lymphoma before appropriate treatment can be started. In this study, NABCT failed to establish a precise histopathological diagnosis in 62 patients suspected to have lymphoma. In this group, the diagnosis was confirmed in 56 cases (90 per cent) after RPS. With germ cell tumours, the main aim of RPS was to identify mixed forms, because small samples provided by NABCT were sometimes insufficient to perform complete histological and immunohistochemical studies[20]. Moreover, both in lymphoma and germ cell tumours, the sensitivity of NABCT is limited by the presence of necrotic or inflammatory areas. Many biopsies are then necessary to obtain adequate samples which increases the morbidity of the procedure.

In patients suspected of having retroperitoneal recurrent neoplastic lymphadenopathy, NABCT provides excellent sensitivity and, therefore, is the method of choice in the first instance[21]. However, lymph nodes smaller than 2 cm, which cannot be sampled by NABCT, are an excellent indication for RPS. In 14 of the 20 patients with retroperitoneal metastatic lymph nodes, the lesions had a diameter smaller than 2 cm. A precise histopathological diagnosis was obtained after RPS in all 14 patients.

RPS is particularly useful when retroperitoneal tuberculosis is suspected because large biopsies enable bacteriological studies to be combined with histology. In one of three patients who had tuberculosis, only bacteriological studies of the samples could confirm the diagnosis.

Retroperitoneal fibrosis is an exceptional indication and most of the diagnoses are made when a lymphoma is first suspected, but because of the technical difficulties in retroperitoneal dissection, RPS is not recommended for this condition.

RPS requires simple and affordable equipment and its feasibility is limited only by major morbid obesity (which accounted for four false-negative results in this study). The success rate is now improved by use of a 23-cm endoscope, which is also used for pericardoscopies (1070 B; Karl Storz). This endoscope, despite dissection difficulties resulting from the long distance between the eye of the operator and the area to be explored, reduces the incidence of these technical failures; since the introduction of the 23-cm endoscope only one false-negative result has been obtained, in an obese patient who had a recurrence of Hodgkin's disease.

Peroperative morbidity was minimal since only one surgical operation was necessary to achieve haemostasis of the sampling area. The left ureteric injury occurred in a young patient who had an extragonadal germ cell tumour and a duplicated ureter surrounded by tumour infiltration (*Fig. 3*).

The sensitivity of RPS is 100 per cent for most pathologies, although in non-Hodgkin's lymphoma the frequent presence of necrotic tissue increases the number of false-negative results. Nevertheless the sensitivity of RPS is superior to that of NABCT in this field. For this reason, the authors strongly believe that when urgent chemotherapy is required for patients suffering from high-grade non-Hodgkin's lymphoma, RPS is the diagnostic procedure of first choice.

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Comparison between the colonic J pouch–anal anastomosis and healthy rectum: clinical and physiological function

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Background Colonic pouch anastomosis after restorative rectal excision obviates much of the early dysfunction which is commonly experienced with the traditional straight coloanal anastomosis. A disadvantage with colonic pouch reconstruction, however, appears to be impaired evacuation.

Methods Distal bowel function was investigated in 30 patients with a colonic J pouch anastomosis at 1 year after surgery and in 39 control subjects.

Results While the degree of urgency and incontinence were similar, the patients with a pouch experienced more difficult evacuation. The maximum volume of the pouch (median 235 ml) and rectum (221 ml) was similar, but the rectum was more compliant (3·5 *versus* 2·6 ml per cmH$_2$O, $P < 0 \cdot 01$). The sensory function in terms of initial sensation of filling, urge to defaecate and maximum distension pressure was impaired in those with pouches. The amplitude of the neorectal and anal canal motility pattern was threefold that of controls. Maximum volume of the pouch was significantly associated with degree of impaired evacuation the larger the volume the more difficult the evacuation.

Conclusion To reduce evacuation difficulty the pouch should not be fashioned too large. No conclusion about optimal pouch size could be drawn. In spite of fundamental physiological differences between a pouch and healthy anorectum, patients with a colonic pouch will usually experience satisfactory clinical bowel function.

Total mesorectal excision is a standard procedure for radical resection of cancers in the low and middle rectum[1]. The majority of the patients can be offered a sphincter-saving procedure and removal of the rectum requires a coloanal anastomosis. It has been reported in several studies[2–4] that reconstruction with a colonic pouch obviates much of the early dysfunction in terms of urgent and frequent bowel movements which is commonly experienced after a traditional straight anastomosis. These symptoms have, at least partly, been attributed to the loss of the rectal reservoir. The superiority of the colonic pouch anastomosis at 1 year after operation compared with the straight anastomosis has been shown in randomized trials[5,6]. A disadvantage with colonic pouch reconstruction, however, appears to be impaired evacuation. A quarter of the patients with a pouch in an early series reported regular need of enemas to evacuate the bowel[7].

The present study determined clinical and physiological characteristics of the colonic pouch–anal anastomosis in comparison with healthy anorectum in controls. The aim was to describe the colonic J pouch as a rectal substitute and to relate evacuation function to physiological variables.

Patients and methods

Patients and controls

A consecutive series of 37 patients all underwent total mesorectal excision and colonic pouch anastomosis for rectal carcinoma. Laboratory follow-up at 1 year was not possible in seven patients because of death from generalized cancer ($n = 2$), death from cerebrovascular disease ($n = 1$), anastomotic stricture despite balloon dilatation ($n = 1$), patient preference ($n = 2$) and because one patient was referred from another region. Thus 30 patients were investigated 1 year after bowel continuity was restored.

The proximal sigmoid was used for the reconstruction in 22 patients leaving the left colic vessels intact. In the remaining eight the inferior mesenteric vessels were divided at their origin, the splenic flexure mobilized and the descending colon used for the reconstruction. The double stapling technique was used for the anastomosis. The colonic pouch was fashioned by folding the colon and creating a side-to-side anastomosis with a linear cutting stapler (90 mm, $n = 23$ and 75 mm, $n = 7$) introduced through the apex of the pouch. The short limb of the J was closed using a linear stapler. All but one patient had a temporary loop ileostomy. Two patients with Dukes 'D' tumours had simultaneous wedge resection of a solitary liver metastasis Three patients had preoperative radiotherapy (25 Gy during the week before surgery). One patient had a pelvic abscess after operation which was treated successfully by transanal drainage. Besides the patient with anastomotic stricture precluding laboratory investigation, anastomotic stricture was successfully dilated in one patient. Five patients had evidence of distant metastases at follow-up, but none was admitted to hospital or withdrawn from the study. There was no local recurrence at 1-year follow-up.

The patients and control subjects answered a questionnaire regarding distal bowel function and medication, and were examined by means of anorectal (pouch) manovolumetry and rigid proctoscopy. The controls were volunteers without incontinence, previous anorectal surgery or symptoms of gastrointestinal disease. *Table 1* shows characteristics of the patients and controls.

Laboratory technique

The manovolumetry method, described in detail elsewhere[8,9], was used to assess the reservoir function of the distal bowel, rectoanal inhibitory reflex and anal canal pressure. Volume changes in the distal bowel, the (neo)rectum, were recorded as a response to isobaric distension at defined distension pressures. A pressure–volume curve was generated by a series of distensions with 10 cmH$_2$O increments, and the sensory thresholds for appreciation of filling and urge to defaecate were noted

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Table 1 Characteristics of patients and controls

	Colonic pouch ($n=30$)	Controls ($n=39$)
Sex ratio (F:M)	11:19	15:24
Age (years)*	68 (47–84)	73 (43–84)
Tumour height above anal verge (cm)*	8 (3–14)	
Dukes stage		
A	8	
B	11	
C	9	
D	2	
Height of anastomosis above anal verge (cm)*	4 (2·5–5·5)	

*Values are median (range)

Maximum volume was taken either as the maximum tolerable volume or the volume at maximum distension pressure (80 cmH_2O) allowed by the device. Compliance (ml per cmH_2O) was calculated as the mean slope in the interval between initial sensation of filling and maximum volume. (Neo)rectal motility was calculated as the quotient between the transient volume decrease in response to a distension pressure of 30 cmH_2O and the maximum volume at that pressure. Anal motility was calculated as the quotient between the mean amplitude of the anal resting pressure oscillation and the mean resting pressure during the manovolumetry study (20 min) The quotients were used because of considerable variability in volume and resting pressure among the individuals The (neo)rectoanal inhibitory reflex was defined as the occurrence of a 20 per cent or more reduction of resting anal pressure in response to (neo)rectal distension.

Evaluation of clinical bowel function

A questionnaire provided the following data.

1. Frequency of bowel movements (per 24 h), calculated as the mean value noted on a 7-day diary card
2. Degree of urgency. Ability to defer defaecation for 30 min was graded as 0, always; 1, often, 2, sometimes; and 3, never.
3. Degree of impaired evacuation. Ability to evacuate the bowel in less than 15 min was graded as 0, always; 1, often; 2, sometimes; and 3, never.
4. Composite score of faecal incontinence. Maximum score was 18 Zero indicated no incontinence. The score was determined from a grid which takes into account both the grade and frequency of incontinence[6].

Statistical analysis

Non-parametric tests were used for comparison of grouped data Coefficients of simple correlations were used to explore the association between the degree of impaired evacuation in the patients with a pouch on the one hand and demographic and physiological variables on the other. In further analysis, logistic regression models were used to adjust for possible confounding factors. In an ordinary logistic regression model, degree of impaired evacuation was dichotomized, using no evacuation difficulty *versus* any degree of evacuation difficulty as the dependent variable. An ordinal logistic regression[10] was also used to utilize the four degrees of impaired evacuation (0, 1, 2, 3) as the dependent variable. Significance was claimed when the P value of a two-sided test was less than or equal to 0·05.

Results

There was no statistical difference between the pouch group and controls in degree of urgency or incontinence score. Frequency of bowel movements was lower in the controls. The patients with a pouch had a significantly higher degree of impaired evacuation and use of medication to evacuate (*Table 2*). The physiological results are shown in *Table 3*. The pouches were less compliant than rectum (*Fig. 1*). The maximum volumes, however, were similar (*Fig. 2*). The median volume of pouches fashioned with a 75-mm stapler was smaller than that of those formed with a 90-mm stapler (195 *versus* 258 ml, $P = 0{\cdot}031$). Sensory function is shown in *Fig. 3*. Higher pressures were required to elicit the sensation of urge ($P < 0{\cdot}01$) and 'maximum' ($P < 0{\cdot}001$) in the patients with a pouch. The pouch volumes at initial sensation and urge were larger ($P = 0{\cdot}032$ and $P = 0{\cdot}021$ respectively). Neorectal motility as well as the motility of the anal canal were increased threefold compared with values in controls. The resting pressure of the anal canal was lower and the squeeze pressure similar compared with those in controls. Maximum volume correlated significantly with impaired evacuation in the patients with a pouch ($P = 0{\cdot}0016$, Spearman rank correlation). *Fig. 4* shows individual pouch volumes in relation to the degree of impaired evacuation.

Both ordinary ($P = 0{\cdot}02$) and ordinal ($P = 0{\cdot}0008$) logistic regression verified maximal volume as a significant factor associated with impaired evacuation when adjusting for possible confounding factors. In addition to maximum volume, the factors entered in the regression models were

Table 2 Clinical bowel function

	Colonic pouch ($n=30$)	Controls ($n=39$)	P
Frequency of bowel movements (per 24 h)*	2·0 (1·4–2·4)	1·1 (1·0–1·4)	<0·001†
Ability to defer defaecation for 30 min (%)			
Always	50	46	0·45†
Often	47	39	
Sometimes	3	15	
Never	0	0	
Ability to evacuate the bowel in less than 15 min (%)			
Always	43	82	<0·001†
Often	30	13	
Sometimes	20	5	
Never	7	0	
Composite score of incontinence (range 0–18)*	2 (1–5)	1 (0–2)	0·074†
No. of patients regularly using enema or suppository to evacuate the bowel	5	0	0·013‡

*Values are median (interquartile range). †Wilcoxon rank sum test, ‡Fisher's exact test

Table 3 Physiological function of the anal canal and (neo)rectum

	Colonic pouch ($n = 30$)	Controls ($n = 39$)	P‡
Resting pressure (cmH_2O)*	53 (41–70)	80 (64–89)	<0·001
Squeeze pressure (cmH_2O)*	195 (160–271)	224 (179–301)	0·28
Anal motility (quotient)*	0.3 (0·2–0·5)	0·09 (0·07–0·1)	<0·001
No. with (neo)rectoanal inhibitory reflex	13	39	
Maximum (neo)rectal volume (ml)*	235 (192–283)	221 (176–256)	0·16
Compliance (ml/cmH_2O)*†	2·6 (1·9–3·4)	3·5 (2·7–4·4)	<0·01
(Neo)rectal motility (quotient)*	0·3 (0·1–0·5)	0·09 (0·07–0·2)	<0·001

*Values are median (interquartile range). †Calculated as the mean slope in the interval between maximum volume and initial sensation of filling of the (neo)rectum. ‡Wilcoxon rank sum test

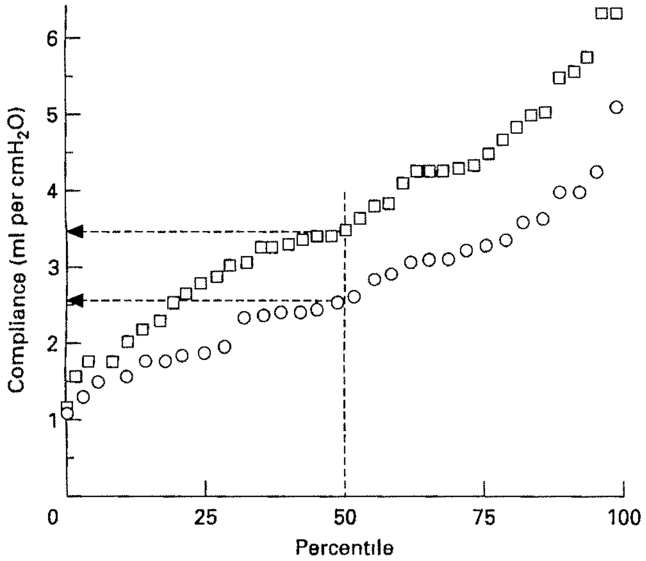

Fig. 1 Percentile plot of individual compliance values for patients with a colonic pouch (○, $n = 30$) and controls (□; $n = 39$) Arrows indicate median values (2·6 and 3·5 ml/cmH_2O respectively, $P < 0·01$, Wilcoxon rank sum test)

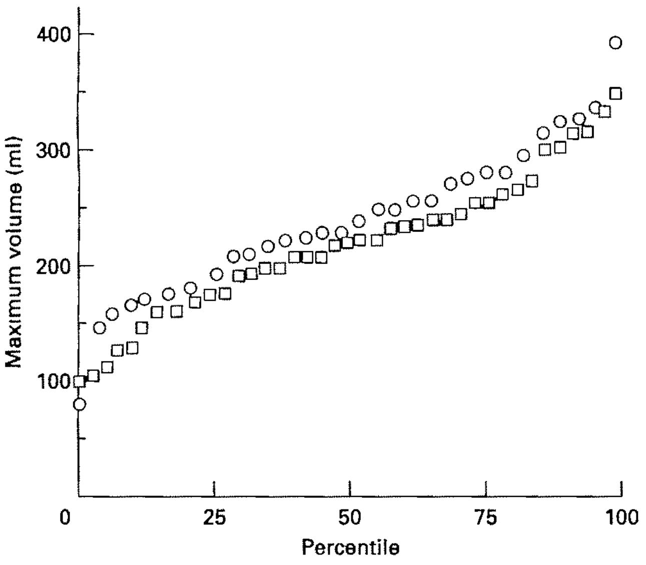

Fig. 2 Percentile plot of individual maximum volumes for patients with a colonic pouch (○; $n = 30$) and controls (□; $n = 39$)

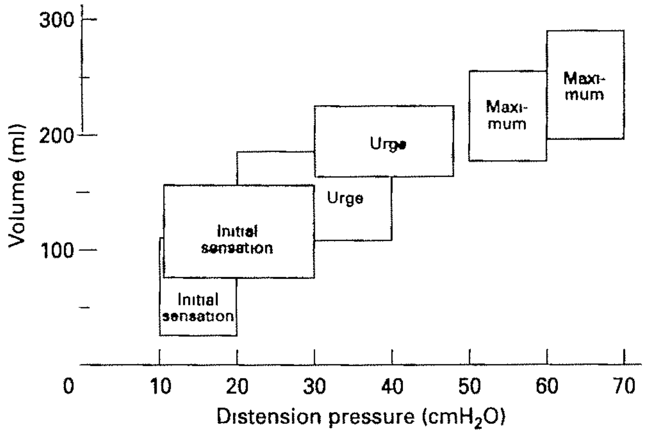

Fig. 3 Threshold values for initial sensation of filling, urge to defaecate and maximum distension pressure and volume. Boxes represent interquartile ranges for patients with a colonic pouch (□; $n = 30$) and controls (□; $n = 39$)

age, sex, part of colon used (sigmoid/descending), height of the anastomosis and the physiological variables in *Table 3*. None of these additional factors individually showed significant effects on degree of impaired evacuation. The smaller volume of pouches fashioned with a 75-mm stapler ($n = 7$) was not associated with significantly better evacuation ($P = 0·33$). Median frequency of bowel movements per 24 h was lower in patients with pouches fashioned from descending colon compared with sigmoid colon (0·9 *versus* 2·1, $P = 0·02$). Urgency, evacuation (including use of enemas or suppositories) or incontinence were, however, similar whichever part of colon was used for pouch construction. Maximum volume, compliance and pouch motility were also similar. The patient with a pelvic abscess had 3 bowel movements per 24 h, but no urgency or evacuation difficulty. His incontinence score was 5, maximum pouch volume 195 ml and pouch compliance 2·9 ml per cmH_2O Anal pressures and results of clinical bowel function in the three patients who had preoperative radiotherapy were similar to those of the main group.

Discussion

The most striking difference in clinical function between patients with a colonic pouch and controls was in their ability to evacuate the bowel. However, 25 of 30 patients with a pouch experienced spontaneous evacuation and

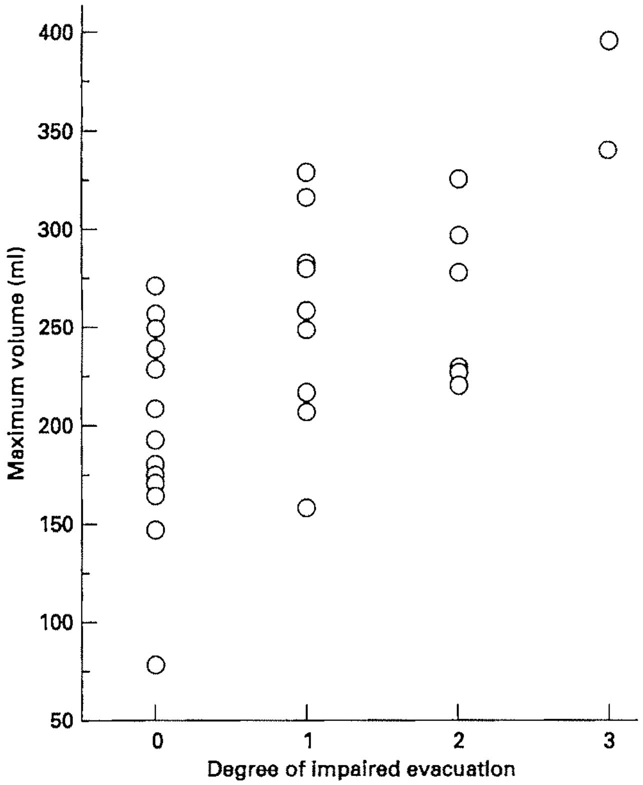

Fig. 4 Individual pouch volumes in relation to degree of impaired evacuation. 0 indicates no evacuation difficulty and 3, complete inability to evacuate the bowel in less than 15 min. $P = 0{\cdot}0016$ (Spearman rank correlation)

two-thirds reported no or only minor evacuation difficulty. The degree of urgency and incontinence appeared similar, findings which are in line with those of Pélissier *et al.*[11]. The numeric difference in frequency of bowel movements may have less clinical importance although it was statistically significant. The study also shows that bowel function was not perfect in control subjects of similar age.

The manovolumetry method has been used to compare ileal pouches with healthy rectum[12]. To describe the reservoir function, volume measurements at defined distension pressures and a calculated compliance value related to the sensory function were used, as proposed by others[13].

Reconstruction with a colonic pouch restored neorectal volume, which is in agreement with a previous assessment of the pouch[2]. The healthy rectum, however, was more compliant. The longitudinal staple lines in addition to the elastic properties and motility of the colonic wall in the pouch may explain this difference. It has been argued that a large pouch may prevent spontaneous evacuation[14]. The significant correlation in this study between maximum volume of the pouch and evacuation may have implications for the surgical technique. Results from the simple correlation may be spurious, but were supported by the regression analyses with adjustment for confounding factors. Because of the small number of observations it was not possible to draw any conclusion about how small the pouch should be fashioned without losing the advantage of less urgency and incontinence.

It may be postulated that impaired evacuation of the pouch is the result of several factors. A rectal substitute fashioned from colon will have impaired sensory function[15], which was also shown in this study. In combination with decreased compliance the sensory deficit may lead to inability to perceive imminent defaecation. Furthermore, 'difficult' evacuation may have other meanings to the patient, such as multiple evacuations, a symptom which appears to be a particular problem also after straight coloanal anastomosis[16]. The motility quotient, which was increased in neorectum compared with healthy rectum, was not significantly associated with the ability to evacuate. This contractibility of the anastomosed colon has been correlated previously with adverse clinical function[17,18], and may reflect irritability in response to distension stimuli rather than propulsive motility. A decreased resting anal pressure is commonly seen after a coloanal anastomosis[19]. Hypermotility of the anal canal, which was apparent in this study, is probably caused by the proximity of the anastomosis. Its relation to poor function has been identified previously[18].

The height of the anastomosis is an important determinant of function with the traditional straight low anastomosis[20]. When a colonic pouch is used, however, it is anticipated that if the anastomosis is fashioned above the anal canal disordered evacuation may occur[14]. Because of the standardized rectal excision in the present patients this variable was not decisive in the present study.

The use of a colonic pouch as a substitute for the rectum restores the anatomy in terms of neorectal volume. To reduce evacuation difficulty the pouch should not be made too large. No conclusion about optimal pouch size could be drawn from this study. In spite of fundamental physiological differences between the pouch and healthy anorectum regarding sensory function, compliance, motility and reflex inhibition, patients with a colonic pouch will usually experience satisfactory clinical bowel function.

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Outcome after multiple colorectal tumours

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Background Patients with primary colorectal cancers have a higher risk of development of second tumours synchronously or metachronously. This special group of patients raise a particular interest in their characteristics and outcome.

Methods The records of 1009 patients with colorectal cancer were scrutinized. A group with multiple cancers was identified. Perioperative investigations, patterns of follow-up, pathological variables and outcome were noted.

Results There were 22 patients with metachronous tumours and 39 with synchronous tumours following 'curative' operations in 20 and 28 respectively. There was no difference in Dukes classification between the two groups. Polyps were associated with metachronous lesions in ten of 22 patients and synchronous lesions in 17 of 39 patients. Five-year survival was 75 per cent for patients with metachronous tumours and only 18 per cent for those with synchronous tumours.

Conclusion In this study patients with metachronous tumours seemed to do very well while those with synchronous lesions did very badly. There were no identifiable demographic or clinical characteristics to account for this. There is a need to study this group of patients and identify factors like tumour biology or host resistance which prevent spread of tumour.

There is an increased risk of development of a second tumour (synchronous or metachronous) in a patient who has been found to have a primary tumour. Host factors, such as genetic defects or impaired immune status, exposure to common environmental risk factors or side-effects of cancer treatments, are the most common explanations for the occurrence of multiple tumours[1]. Two or more lesions may arise simultaneously or at a variable time interval, ranging from months to several years. Warren and Gates[2] defined synchronous (simultaneous) cancers of the large bowel as tumours that present a definite picture of malignancy, each of which must be distinct with no possibility of one being the metastasis of the other. Moertel *et al.*[3] have defined synchronous tumours as those which are recognized within an arbitrary period of 6 months after diagnosis of the primary tumour. Tumours occurring after this time are classified as metachronous provided they are not recurrences at the anastomosis or metastatic from the original tumour. The discovery of multiple tumours depends on the diagnostic preoperative and postoperative investigations, the type of operation and the follow-up regimen[4,5]. This study describes the findings in 61 patients with multiple tumours who were treated under the care of one surgeon.

Methods

The medical records of 1009 patients with colorectal carcinoma presenting between May 1980 and September 1995 were reviewed and scrutinized. The perioperative investigative procedures, details of the operations and histopathology, the pattern of follow-up and final outcome were noted. The tumour sites were expressed as right sided, left sided or rectal[6]. All patients underwent either preoperative or postoperative colonoscopy or double contrast barium enema examination. After operation the patients were reviewed every 3 months for 2 years, 6 monthly for 5 years and annually for life. The stage of the tumours and the grade of malignancy were recorded. The association of polyps with these tumours was examined and their incidence and types were noted.

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Results

Metachronous tumours

Twenty-two patients had a total of 47 tumours. One patient had a synchronous tumour in addition to two metachronous tumours and two patients had three metachronous tumours. There were equal numbers of men and women. All tumours were adenocarcinomas with the exception of one malignant carcinoid tumour. The mean age was 60·4 (range 35–82) years at the time of diagnosis of the first tumour and 67·3 (range 54–85) years at the time of diagnosis of the second tumour.

Fifteen of 22 patients presented with symptoms and were diagnosed by rigid sigmoidoscopy and/or double contrast barium enema or at emergency laparotomy. Six patients were diagnosed at follow-up colonoscopy and one had a rise in carcinoembryonic antigen level. The interval between presentation with the original tumour and the second tumour ranged from 1 to 39 years (less than 5 years in ten patients, 5–10 years in five patients and more than 10 years in seven patients). The tumours were evenly distributed between right (21) and left (20) colon and there were six tumours in the rectum. Twenty of the operations were defined as curative. The operations performed are shown in *Fig. 1.*

The first tumours were mostly of average differentiation and only one was a poorly differentiated Dukes B adenocarcinoma. The second metachronous tumours were of average grade malignancy in 14 cases, five were poorly differentiated and three not recorded. There were two patients who developed a third tumour. One was a malignant carcinoid tumour and the other was a poorly differentiated adenocarcinoma in a severely dysplastic polyp.

Polyps of variable size (2–15 mm diameter) were found in association with the first tumour in half the patients. In eight patients they were metaplastic and in four they were tubular adenomas. Subsequently polyps were found by follow-up colonoscopy or at a second operation in ten patients (four metaplastic, one metaplastic and multiple villous adenomas, five tubular adenomas). There were two

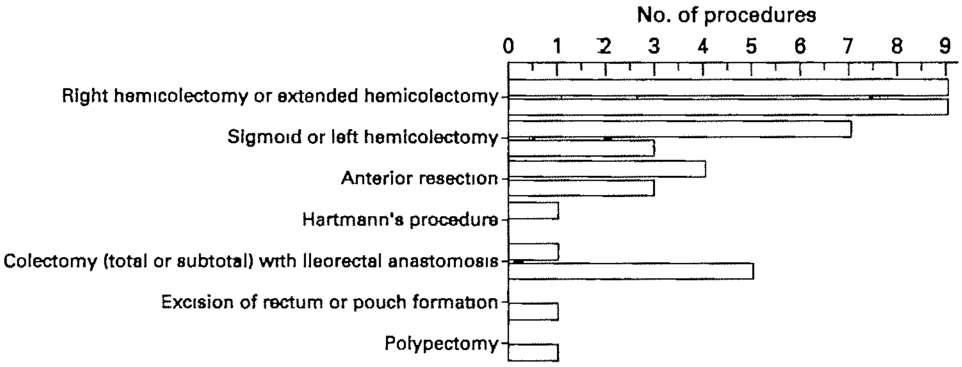

Fig. 1 Operations for metachronous tumours. □, First tumour; □, second tumour

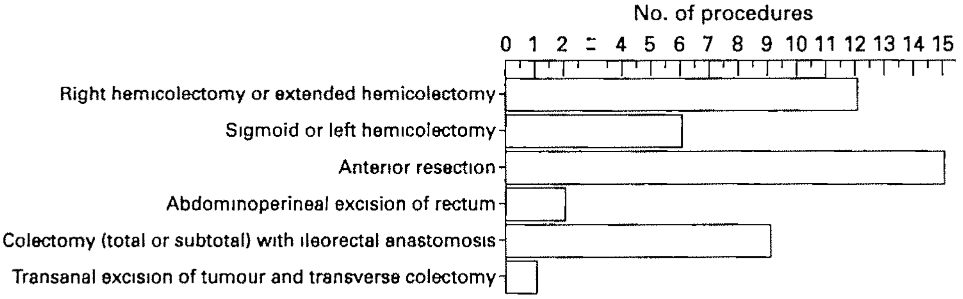

Fig. 2 Operations for synchronous tumours

Dukes A, ten Dukes B and five Dukes C primary tumours, compared with six Dukes A, nine Dukes B, seven Dukes C and one carcinoid identified at second operation. There were no records for five patients treated elsewhere.

All patients survived more than 2 years and three-quarters survived more than 5 years. Four of the deaths were due to cancer and one patient was tumour free. The second tumours in these patients were diagnosed at intervals of 2, 9, 10 and 15 years after the original surgery. Of the six patients who did not complete 5-year follow-up and are alive, five have been followed for more than 4 years and one patient for 1·9 years.

Synchronous tumours

Thirty-nine patients (27 men and 12 women) had a total of 78 tumours. The mean age at presentation was 72·5 (range 41–91) years. All tumours were adenocarcinomas.

The diagnosis of a synchronous tumour was made at operation in 27 patients, before operation in six and after operation in six. Before operation the tumours were diagnosed at colonoscopy as were two of those identified after operation. The other four tumours found after surgery produced symptoms. One patient was admitted as an emergency with obstruction by a distal colorectal tumour. The authors' practice is to subject such patients to colonoscopy within 6 months after operation. Two patients had routine colonoscopies, while two developed signs and symptoms which brought their postoperative investigation forward. One had an incomplete colonoscopic examination of the transverse colon and no barium enema was performed. This patient presented with a mass in the right iliac fossa. There was an even distribution of the tumours in the two sides of the colon and rectum; 28 were right sided, 23 were left sided and 27 were rectal. The number of patients with at least one lesion in the right colon was 23, in the left colon 21 and in the rectum 21. The types of operation performed on patients with synchronous tumours are shown in *Fig. 2*.

Although operations were curative in 28 of 39 patients, only five of these 28 patients survived more than 5 years. Ten patients who did not complete 5-year follow-up have been followed for a mean of 3·2 years. The stage of the tumours in these patients, taking the most advanced, was Dukes A (five patients), Dukes B (13) and Dukes C (ten). Sixty-one of the 78 tumours were of average-grade malignancy, ten were poorly differentiated and seven not recorded.

Polyps were found in association with synchronous tumours in 17 patients (12 tubular adenomas, in three of which there was a villous component, and five metaplastic polyps).

Discussion

The incidence of metachronous cancers in the colon and rectum varies between 2 and 6 per cent. In one report the incidence was biphasic, with a peak during the first 4–5 years and another after 10–12 years[7]. The authors considered the first peak to represent synchronous carcinomas or adenomas which went unnoticed at first presentation. This is not in accordance with Moertel's definition (6 months). In the present series of 1009 patients with colorectal cancer treated between May 1980 and September 1995 the incidence of metachronous tumours and synchronous tumours was 2·2 and 3·9 per cent respectively.

In a previous study of 555 patients with colorectal tumours, 128 patients had palliative resection and three-quarters died within 2 years[6]. In the present study of multiple colorectal cancers, all tumours were resectable and only one operation in the synchronous group and two in the metachronous group were performed as an emergency. In the synchronous group although operations were considered curative in 28 of 39 patients, outcome was poor with only five of these patients surviving more than 5 years. However, Dukes staging of these tumours was unfavourable with ten classified as Dukes' C and 13 as Dukes' B.

In a report[8] from St Mark's hospital in 1975, only 40 per cent of synchronous colorectal lesions were identified before operation by barium enema. Colonoscopy may not be successful in all cases before operation; in one series it was possible in only 32 per cent of patients[5].

Despite all investigative procedures there will inevitably be a few patients whose synchronous tumours will not be detected at the time of operation for their first tumour. Colonoscopy, carried out at operation where possible, as well as within 3–6 months after operation, will hopefully further decrease the incidence of delayed diagnosis of synchronous tumours. It is for this reason that Moertel *et al.*[3] developed their definition (less than 6 months) for such tumours and even then a few will still be missed.

For patients with metachronous lesions the mean age at presentation of the first tumour in this report was 60·4 (range 35–85) years compared with 73 (range 21–105) years for 555 patients with single carcinomas[6]. This is in keeping with previous reports[9].

The presence of polyps in patients with multiple tumours of the colon and rectum is of particular interest. Twenty-nine of the 61 patients (48 per cent) with multiple colorectal tumours had polyps found at some time. In 13 patients the polyps were metaplastic (hyperplastic), in 19 patients they were tubular adenomas with only three showing a villous component in the synchronous group. Metaplastic polyps have long been considered as non-neoplastic; however, recent reports suggest an association with dysplasia and carcinoma[9,10].

Patients with a single polyp have a 7–11 per cent chance of developing colonic carcinoma, rising to 18–21 per cent if multiple polyps are found[1]. Benign polyps occur in 12–25 per cent of patients with single cancers. The incidence of benign neoplastic polyps in patients with synchronous cancers may be as high as 56–86 per cent[9] but most series report a lower incidence of 38–40 per cent[12]. This seems to depend on the methodology of reporting and inclusion or exclusion of small (less than 5 mm) adenomatous polyps and/or diminutive metaplastic polyps. It is believed that second colonic cancers, especially metachronous tumours, are more closely associated with polyps than are single colonic cancers. In one series, 24 of 41 patients with synchronous tumours and 16 of 26 metachronous lesions had associated polyps[11].

In this series the first tumours were evenly distributed between right and left colon. However, in a cancer registry-based study, the Surveillance Epidemiology and End Result program USA, the survival patterns were investigated in 1396 patients with metachronous tumour noted in 143 283 with primary colorectal cancers. In this study metachronous tumours developed more often following left colonic tumours[1].

Fig. 3 clearly shows the poorer outcome in patients with synchronous tumours as compared with those in the metachronous group. The finding that patients with metachronous tumours do very well after surgery for the second tumour is of great interest and, if it is confirmed by other studies, it may subsequently be possible to identify factors in this group, such as the tumour biology or the host resistance, which prevent spread of the tumour[4]. In this series, analysis of the demographic and clinical characteristics of patients with metachronous and synchronous tumours did not reveal significant differences to account for the good outcome in the former group and the poor outcome in the synchronous group. The only observation of relevance was the presentation of the metachronous group at an earlier age than the synchronous group.

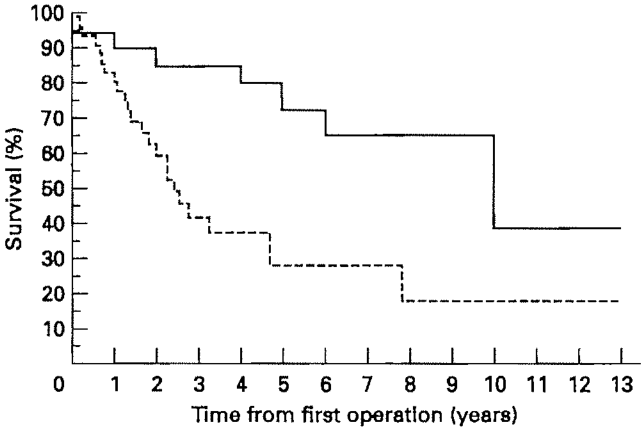

Fig. 3 Survival curves for patients with metachronous (——) and synchronous (– – –) tumours

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Long-term results of preoperative radiation therapy alone for stage T_3 and T_4 rectal cancer

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Background There has been a resurgence of interest in the use of preoperative radiation therapy, with or without chemotherapy, for locally advanced rectal cancer. The purpose of this study was to analyse the time course and pattern of failure for 74 patients with clinical stage T_3 or T_4 (cT_{3-4}) rectal cancer treated with preoperative radiation therapy for whom long-term follow-up was available.

Methods Seventy-four patients with cT_{3-4} rectal cancer received a median of 45·0 Gy radiation alone followed by surgery 4–8 weeks later. Median follow-up was 90 months; two-thirds of patients were followed for at least 60 months.

Results Following radiation therapy the pathological stage was 4 per cent pT_0, 26 per cent pT_{1-2} and 70 per cent pT_{3-4}. Thirty-two per cent had involved lymph nodes. The actuarial 5-year rates of local control, freedom from distant metastasis and disease-specific survival were 80, 64 and 73 per cent respectively. The corresponding 10-year rates were 73, 51 and 50 per cent. Median times to detection of local and distant recurrence were 34 and 24 months respectively. Eighty per cent of local recurrences were detected within 54 months; 80 per cent of distant recurrences were detected within 57 months.

Conclusion In this analysis, the time to detection of both local and distant recurrences following preoperative radiation therapy for advanced rectal cancer was surprisingly long. Almost 5 years (57 months) of follow-up were required to detect 80 per cent of all failures. The 5-year local control rate of 80 per cent compares favourably with that achieved by more aggressive chemoradiation regimens for fixed cancers; however, the high distant failure rate with radiation therapy alone suggests that adjuvant systemic therapy should be investigated.

There is increasing pressure on clinical researchers to demonstrate improvements in the ability to cure cancer. Often, promising early results from clinical trials are published after relatively short follow-up. However, such results do not obviate the need for publication of mature data so that conclusions may be drawn regarding ultimate treatment efficacy.

An example of the need for long-term follow-up information may be found in the treatment of locally advanced rectal cancer, for which optimal management remains controversial. The efficacy of adjuvant therapy for rectal cancer is judged against the results obtained with surgery alone. Historically, 80 per cent of pelvic recurrence was detected within 2 years of surgery[1,2]. However, the use of adjuvant therapy may alter both the pattern and time course of disease recurrence, such that early reporting of treatment results (i.e. after only 2 years of follow-up) may risk overestimation of treatment efficacy.

Recent published studies of preoperative radiation therapy with or without chemotherapy for advanced rectal cancer have relatively short median follow-up (range 26–38 months)[3–6]. In contrast, the institutional approach to management of rectal cancer at Thomas Jefferson University Hospital began over 20 years ago. Long-term follow-up data (median 90 months) are now available for patients who received preoperative radiation therapy for clinical stage T_3 or T_4 rectal cancer. The purpose of this study was to analyse the pattern and time course of disease failure among these patients.

Patients and methods

A total of 189 patients with clinical stage T_3 or T_4 (tethered or fixed) rectal cancer at presentation were treated with high-dose preoperative radiation therapy between 1976 and 1993. Seventy-four patients received whole pelvic radiation alone to a median dose of 45 (range 40–45·8) Gy and are the subjects of this study. Of the remaining 115 patients, 82 received radiation therapy alone to a median dose of 55·8 Gy and 33 received chemoradiotherapy, consisting of 5-fluorouracil (5-FU)-based chemotherapy and a median radiation dose of 55·8 Gy. The latter two groups of patients have been the subject of previous publications[7,8].

Pretreatment evaluation included physical examination, proctosigmoidoscopy with biopsy, radiography, and colonoscopy or barium enema when feasible. All patients had a blood count and liver function tests and either a liver–spleen scan or computed tomography (CT) of the abdomen and pelvis to evaluate the presence of liver metastases. Additional diagnostic studies included estimation of carcinoembryonic antigen level.

After treatment, all patients were followed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. All patients were seen either in joint clinics or alternating visits by the radiation oncologist and surgeon. Routine follow-up studies included annual radiography, colonoscopy and blood studies. Follow-up CT scans were obtained only if warranted by the clinical situation.

Of the 74 patients, 39 (53 per cent) were men and 35 (47 per cent) were women, of median age 62 years. The level of tumour in the rectum was measured from the anorectal ring to the lowest extent of the lesion. Twenty-three patients (31 per cent) had tumours at the level of 0–3 cm, 32 (43 per cent) at more than 3 to 6 cm, and 15 (20 per cent) at more than 6 to 12 cm. Three additional patients (4 per cent) had tumours at the rectosigmoid junction, 13–15 cm from the anorectal ring.

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Tumour level was unknown for one patient Forty-four patients (59 per cent) had clinically tethered tumours at presentation cancers with limited mobility secondary to extrarectal spread but still mobile in at least one direction (clinical T_3). Thirty patients (41 per cent) had clinically fixed tumours at presentation – firmly adherent to adjacent structures and immobile (clinical T_4).

Radiation therapy

All patients received pelvic radiation therapy to a median dose of 45·0 Gy using a four-field box technique. All fields were treated daily, and fraction size ranged from 1·8 to 2·5 (median 1·8) Gy daily. Details of the radiation therapy regimen have been published previously[7,8].

Surgery

Surgery was carried out 4–8 weeks after completion of radiation therapy. Twenty-one patients (28 per cent) had an abdominoperineal resection and ten (14 per cent) underwent low anterior resection. Thirty patients (41 per cent) required a combined abdominal and trans-sacral approach. Nine patients (12 per cent) underwent coloanal anastomosis and four (5 per cent) had full-thickness local excisions. All patients had negative longitudinal and circumferential margins of resection.

Statistical analysis

Median follow-up was 90 (range 3–223) months Seventy-five per cent of patients were followed for at least 42 months, and two-thirds for at least 60 months. Actuarial curves for local control, freedom from distant metastasis and disease-specific survival were calculated with the Kaplan–Meier method[9]. Univariate analysis was performed using the log rank test[10].

Results

After operation patients were staged by means of the 1992 American Joint Committee on Cancer tumour node metastasis (TNM) system[11]. The pathological stage of the tumours by clinical stage is shown in *Table 1*. Of the total group of 74 patients, three tumours (4 per cent) were pathological stage T_0 (pT_0), 19 (26 per cent) were pT_{1-2} and 52 (70 per cent) were pT_{3-4}. Thirty-two per cent of the total group had involved lymph nodes identified in the resection specimen. The distribution of postoperative histological stages was similar in both clinical T_3 (cT_3) and cT_4 categories.

Local control

The crude local failure rate was 20 per cent (15 of 74 patients). The median time to local recurrence was 34 months. Eighty per cent of local failures were detected within 54 months (*Fig. 1*). The overall 5-and 10-year local control rates were 80 and 73 per cent respectively (*Fig. 2*). Local control was analysed as a function of clinical stage (cT_3 *versus* cT_4), pathological T stage following radiation therapy (pT_{0-2} *versus* pT_{3-4}) and N stage following radiation therapy (pN_0 *versus* pN^+), but no significant differences were observed (*Table 2*).

Table 1 Histopathological stage after radiotherapy

Group	*n*	pT_0	$.pT_{1-2}$	pT_{3-4}	pN_0	pN^+	pN unknown
All patients	74	3 (4)	19 (26)	52 (70)	46 (62)	24 (32)	4 (5)
cT_3	44	1 (2)	12 (27)	31 (70)	26 (59)	15 (34)	3 (7)
cT_4	30	2 (7)	7 (23)	21 (70)	20 (67)	9 (30)	1 (3)

Values in parentheses are percentages. pT, pathological tumour stage; pN, pathological node stage, cT, clinical tumour stage

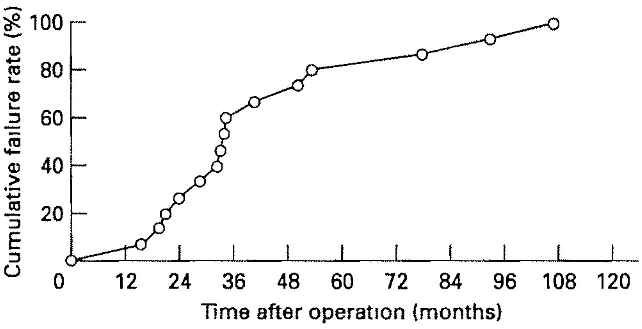

Fig. 1 Time to presentation of local recurrence in 15 of the 74 patients

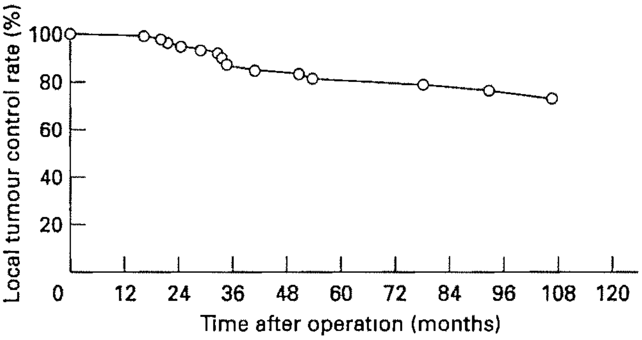

Fig. 2 Overall actuarial rate of local tumour control

Table 2 Actuarial local control rates

	No. of patients	Local control rate (%)	
		5 years	10 years
Overall	74	80	73
Clinical tumour stage			
cT_3	44	82	74
cT_4	30	78	70
Pathological tumour stage			
pT_{0-2}	22	84	84
pT_{3-4}	52	76	67
Pathological node stage			
pN_0	46	85	79
pN^+	24	74	59

Distant metastases

The crude distant failure rate was 42 per cent (31 of 74 patients). The median time to the development of distant metastases was 24 months. Eighty per cent of distant metastases were detected within 57 months (*Fig 3*).

The overall 5- and 10-year actuarial rates of freedom from distant metastases were 64 and 51 per cent respectively (*Fig. 4*). Freedom from distant metastases was analysed as a function of clinical stage (cT_3 *versus* cT_4),

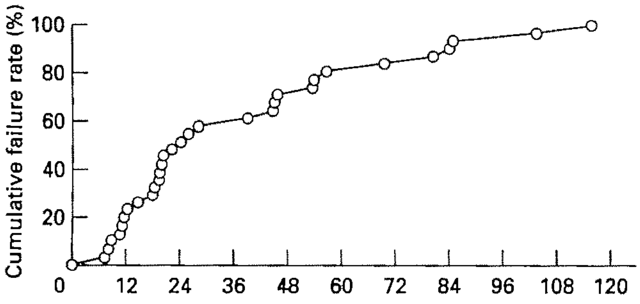

Fig. 3 Time to presentation of distant metastasis in 31 of the 74 patients

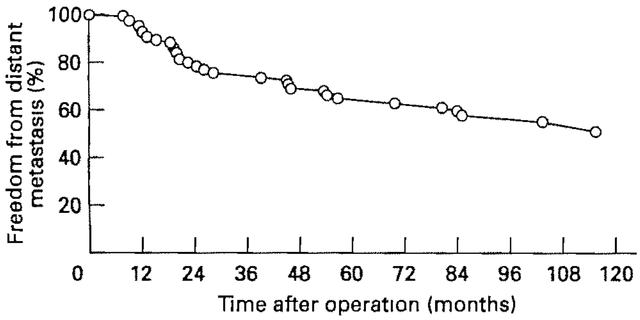

Fig. 4 Overall actuarial rate of freedom from distant metastases

Table 3 Actuarial rates of freedom from distant metastasis

	No. of patients	Rate of freedom from distant metastasis (%)	
		5 years	10 years
Overall	74	64	51
Clinical tumour stage			
cT_3	44	70	55
cT_4	30	55	42
Pathological tumour stage			
pT_{0-2}	22	85	67
pT_{3-4}	52	55	43*
Pathological node stage			
pN_0	46	70	57
pN^+	24	54	42

*$P<0{\cdot}07$ (pT_{3-4} *versus* pT_{0-2}, log rank test)

pathological T stage following radiation therapy (pT_{0-2} *versus* pT_{3-4}) and N stage following radiation therapy (pN_0 *versus* pN^+) (*Table 3*). There was no significant difference in the rate of freedom from distant metastases compared with clinical stage or pathological N stage. However, there was a trend towards a lower rate of freedom from distant metastases among patients with high pathological T stage.

Disease-specific survival

The crude mortality rate from rectal cancer was 42 per cent (31 of 74 patients). The overall 5- and 10-year disease-specific survival rates were 73 and 50 per cent respectively. The 10-year actuarial disease-specific survival rate was 66 per cent for patients with cT_3 and 31 per cent for those with cT_4 tumours ($P<0{\cdot}05$). For patients with pT_{0-2} tumours, the 10-year actuarial disease-specific survival rate was 65 per cent, compared with 46 per cent for those with pT_{3-4} lesions ($P<0{\cdot}08$). Patients who were pN_0 following radiation therapy had a 64 per cent 10-year actuarial disease-specific survival rate, compared with 31 per cent for those who remained pN^+ ($P<0{\cdot}02$).

Toxicity

The main acute morbidity of preoperative radiation therapy was gastrointestinal; the rate of Radiation Therapy Oncology Group grade 3 or 4 acute gastrointestinal toxicity was 5 per cent. There was no grade 3 or 4 acute haematological or skin toxicity. Three patients (4 per cent) had severe late gastrointestinal toxicity. One developed small bowel obstruction with no evidence of recurrent cancer and underwent surgery for lysis of adhesions. The second required a colostomy despite initial sphincter preservation because of persistent severe diarrhoea. The third patient developed severe radiation proctitis necessitating a colostomy.

Discussion

Few authors have reported long-term results of preoperative radiation therapy followed by surgery for locally advanced rectal cancer[3-6,12,13]. Older publications such as those by Emami *et al.*[12] and Dosoretz *et al.*[13] give a minimum follow-up of 36 and 40 months respectively, but recent reports[3-6] tend to have much shorter follow-up ranging from a median of 26 to 38 months. The present series has long-term follow-up data, with a median follow-up 90 months.

Long-term follow-up is critical because in this study the most striking finding was the length of time to detection of both local and distant disease recurrence. A commonly quoted statistic is that 80 per cent of recurrences will be detected within 2 years of treatment for rectal cancer[1,2]. However, this value was derived from patients treated historically with surgery alone. The median interval to local recurrence in the present series was 34 months, and 80 per cent of local recurrences were not detected until 54 months. Similarly, the median interval to detection of distant metastases was 24 months, and 80 per cent were not detected until 57 months. In addition, between 5 and 10 years there was a large fall in the disease-specific survival rate of the overall group, from 73 per cent at 5 years to 50 per cent at 10 years. Such an observation is possible only after analysis of long-term follow-up information.

A second important finding in this analysis was the good long-term local control rate with preoperative radiation therapy alone for clinically fixed (cT_4) rectal cancers. The 5-year actuarial local tumour control rate of 78 per cent compares favourably with that in other published results of preoperative radiation therapy or chemoradiation for fixed or 'irresectable' rectal cancers. Emami *et al.*[12] reported their experience with preoperative radiation therapy (45–50 Gy) followed by complete resection in 26 patients. The crude local control rate was 80 per cent with a minimum follow-up of 36 months. Dosoretz *et al.*[13] reported local control in eight of 13 patients with fixed rectal cancer treated with 40–52 Gy of preoperative radiation therapy with a minimum follow-up of 40 months. Willett *et al.*[3] observed a 5-year actuarial local control rate of 76 per cent among 28 patients treated with 50·4 Gy before operation. Median follow-up was 38 months and the 5-year actuarial disease-specific survival rate was 66 per cent.

Institutional trials of preoperative chemoradiation, usually a combination of radiation therapy with 5-FU, have yielded mixed results. Among 16 patients with fixed rectal cancer, Chan *et al.*[4] observed a 38 per cent actuarial 2-year local failure rate following preoperative radiation therapy (40 Gy in 20 fractions) and concurrent 5-FU–mitomycin C chemotherapy followed by resection. In contrast, Weinstein and colleagues[5] reported a 97 per cent crude local control rate among 37 patients with tethered cT_3 or T_4 rectal cancer treated with preoperative chemoradiation (45 Gy radiation therapy plus infusion of 5-FU) followed by surgery with or without intraoperative radiation therapy. All local failures occurred in patients who did not receive intraoperative irradiation, suggesting that the overall local control rate may have been due to the high total dose of local radiation rather than the addition of chemotherapy. However, median follow-up for this group was only 36 months[5]. Similarly, Rich *et al.*[6] reported a 96 per cent crude local control rate among 77 patients with clinical T_3 rectal cancer treated with preoperative chemoradiation therapy, with a median follow-up of 27 months. Although these early results represent an impressive local control rate for relatively advanced tumours, a decrease in the local control rate with continued follow-up could be expected based on the present study. Investigators should be encouraged to publish long-term results of current trials when available.

It is evident from the present study that distant metastases are a significant problem for patients with cT_3 and cT_4 rectal cancer. This is especially true for patients who remain in pathological stage T_3 or T_4 following preoperative radiation therapy, for whom the 5- and 10-year actuarial rates of freedom from distant metastases were only 55 and 43 per cent respectively. However, even among patients who are pT_{0-2} following preoperative radiation therapy, only 67 per cent remain free of distant metastases at 10 years.

Such findings substantiate the need for effective systemic therapy in conjunction with radiation therapy and surgery in the management of locally advanced rectal cancer. Currently, the European Organization for Research and Treatment of Cancer is conducting a randomized prospective trial investigating the utility and sequencing of 5-FU–leucovorin chemotherapy with preoperative radiation therapy for resectable T_{3-4} tumours.

In summary, the interval to both local and distant disease recurrence is prolonged following preoperative radiation therapy for locally advanced rectal cancer. This mandates careful long-term follow-up of patients and the reporting of the most mature data possible in order to avoid overestimation of treatment efficacy. Preoperative radiation therapy alone for cT_{3-4} rectal cancer provides acceptable local disease control, but distant metastases remain a problem. In patients with coexisting medical problems, preoperative radiation therapy alone is an acceptable treatment. However, for healthy patients with cT_{3-4} rectal cancer, more aggressive treatment strategies may be warranted.

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Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis

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Background Functional outcome after rectal excision with coloanal anastomosis is improved by construction of a colonic J pouch. Present prospective randomized studies lack follow-up beyond 1 year. The aim of this study was to assess the clinical outcome at both short- and long-term follow-up.

Methods Forty patients with low rectal cancer were randomized prospectively to either J colonic pouch–anal anastomosis or a straight coloanal anastomosis. Clinical assessments were performed 3, 12 and 24 months after colostomy closure using a standard questionnaire and physical examination.

Results There was no significant difference in the complication rate between the two groups. There was a significant ($P < 0{\cdot}01$) improvement in frequency of defaecation at 3, 12 and 24 months for patients with a reservoir. Similarly, fragmentation (clustering of stools) was significantly less at 3 and 12 months ($P < 0{\cdot}01$) in the reservoir group, and incontinence occurred less frequently in the first year ($P = 0{\cdot}09$). By 24 months no patient in either group suffered from major or minor incontinence.

Conclusion The functional improvement gained from a colonic reservoir in coloanal anastomosis continues to benefit the patient for at least 2 years.

Since the introduction of endoanal anastomosis[1] and technical advances with stapling devices, the need for abdominoperineal resection for low-lying cancers of the rectum has gradually diminished. The application of coloanal anastomosis has not compromised the oncological results[2,3]. However, low colorectal and coloanal anastomosis often give suboptimal functional results, especially in the 6–18 months after surgery. Disturbances in stool frequency and urgency appear to be a function of the neorectal capacity and are inversely related to the length of the rectal stump. Incontinence is often related to anal sphincter injury[4–6].

To ameliorate the problems associated with reduced neorectal capacity, the colonic J pouch was introduced[7]. Many retrospective and, more recently, three randomized prospective studies have shown a superior functional result with a colonic reservoir[8–11]. These prospective studies[9–11] reported results at 1 year, during which patients with a straight coloanal anastomosis undergo adaptation. The aim of the present study was to investigate both the short- and long-term improvements in functional results with a reservoir compared with a straight coloanal anastomosis.

Patients and methods

Forty-two consecutive patients with rectal carcinoma were recruited over 3 years. Informed consent was obtained. Two patients were withdrawn, one due to a megacolon and one because a renal cell carcinoma required simultaneous nephrectomy. Thus, 40 patients were randomized during operation by means of sealed envelopes into two groups (straight anastomosis, $n = 20$, pouch, $n = 20$). In two patients randomized to receive a pouch, a reservoir could not be constructed owing to inadequate reach from a foreshortened mesentery. Pouch construction would have led to excessive tension following the pouch–anal anastomosis. One patient having a straight anastomosis failed to have colostomy closure.

Surgical technique

All patients received intravenous antibiotics (ceftriaxone and metronidazole) 1 h before incision. Resection of the rectum was done by the abdominotrans-sphincteric approach[12] and the splenic flexure and transverse colon were mobilized in all patients. Either the descending or proximal sigmoid colon was used for anastomosis in all cases. To construct the pouch, a side-to-side anastomosis with a GIA-50 staple gun (US Surgical, Norwalk, Connecticut, USA) was introduced through a colotomy at the apex of the J. Excess colon at the distal short limb of the J was excised. In half the patients the coloanal anastomosis was stapled with an EEA stapler (US Surgical). All patients had a protective proximal colostomy.

Functional assessment

Bowel function was evaluated prospectively after colostomy closure at 3, 12 and 24 months by the same senior surgeon. A standard questionnaire was used which included: (1) frequency of bowel movements per 24 h; (2) urgency (inability to defer defaecation for at least 10–15 min); (3) continence according to the Kirwan–Fazio classification[13]; and (4) use of laxatives for either constipation or bowel evacuation.

Statistical analysis

Nominal variables were analysed with the χ^2 or Fisher's exact test. Student's t test was used to compare differences for the quantitative variables. Mann–Whitney's non-parametric U test was used to confirm the t test. Statistical significance was defined as $P < 0{\cdot}05$.

Results

The patients' clinical characteristics are shown in *Table 1*. There was no postoperative death. Two patients having a straight anastomosis developed pelvic sepsis, and one in the pouch group had this complication. A summary of the

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Table 1 Clinical characteristics

	Coloanal anastomosis ($n = 19$)	J pouch ($n = 18$)	P*
Sex ratio (M:F)	14·5	12:6	n.s.
Mean (range) age (years)	59 (40–82)	56 (42–75)	n.s.
Mean (range) tumour height above anal verge (cm)	5·9 (4–12)	5·0 (3·5–10)	n.s.
Mean (range) anastomotic height above anal verge (cm)	2·3 (1 5–4·0)	1·7 (0·5–3·5)	<0·05
Technique (hand-sewn:stapled)	9.10	10:8	
Adjuvant radiotherapy	9	10	n.s.

n s , Not significant. *χ^2 or Fisher's exact test

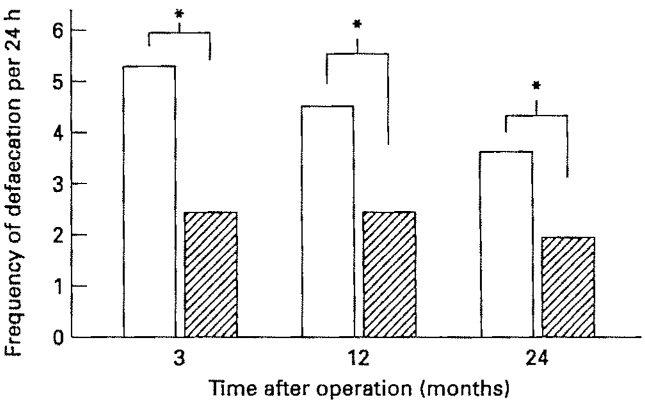

Fig. 1 Frequency of defaecation in patients receiving a straight coloanal anastomosis (□) or a J pouch (▨). *$P < 0·01$ (Student's t and Mann–Whitney U tests)

Table 2 Clinical results

	3 months		12 months		24 months	
	Coloanal anastomosis ($n = 19$)	J pouch ($n = 18$)	Coloanal anastomosis ($n = 16$)	J pouch ($n = 15$)	Coloanal anastomosis ($n = 12$)	J pouch ($n = 13$)
Urgency	12	4*	3	2	0	1
No. of patients with four or more bowel movements per day	12	2*	11	2*	6	2
Laxative use	0	1	1	1	1	1
Major and frequent soiling	5	1	2	0	0	0

*$P < 0·01$ (χ^2 test)

postoperative functional outcome is shown in *Table 2*. Frequency of bowel movements is shown in *Fig. 1*.

At 3 months one patient in the pouch group experienced incontinence, compared with five having a straight anastomosis. This difference was not statistically significant. No patient in either group was incontinent of faeces at 2 years.

Discussion

Numerous studies have demonstrated that, by increasing the neorectal capacity, superior functional results with respect to frequency of defaecation, urgency and incontinence can be obtained after rectal resection[7–11]. However, studies lack follow-up beyond 1 year[9–11].

Many of the initial functional disturbances following straight coloanal anastomosis improve with time, especially during the first year. This improvement is seen as a consequence of adaptive changes in the neorectum. As shown in this study, a significant reduction in frequency of defaecation continues with a colonic pouch for at least 2 years.

The term 'frequency' does not reflect adequately the troublesome 'fragmentation' or 'clustering' associated with bowel evacuation. This interferes with both the employment and social lifestyle of the patient. Fragmentation was more prevalent in patients with a straight coloanal anastomosis. In this study, at all three follow-up intervals, more than half the patients having a straight anastomosis experienced four or more motions in 24 h. This was in contrast to a minority of those receiving a reservoir at 1 and 2 years. The disturbances associated with both frequency and fragmentation are ameliorated in patients with a reservoir, who benefit from an increase in compliance and maximum tolerated volume[7,14].

In contrast to previous studies[9,11] which have shown a significant improvement in incontinence with a J colonic pouch, the difference was not statistically significant in the present study. The small population size and also the significantly lower mean anastomotic height for patients in the reservoir group, which has been shown to influence anal continence adversely, may explain the lack of statistical difference.

The superior functional results with a colonic reservoir following coloanal anastomosis are not limited to the first year and continue to be significant for defaecation frequency and fragmentation for at least 2 years. Also, a colonic reservoir can decrease the incidence of incontinence during the first year which has significant implications for patients with cancer, who may have limited longevity.

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Short note

Soluble protein encoded by CD44 variant exons 8–10 in the serum of patients with colorectal cancer

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CD44 is a widely expressed cell surface glycoprotein, and has been postulated to be a cell adhesion molecule involved in extracellular matrix binding, cell migration and lymphocyte recirculation[1]. The CD44 molecule exists in multiple isoforms produced by the alternative splicing of ten exons encoding parts of the extracellular domain. There have been several reports on the expression of variant exons of CD44 in human cancers[1,2], particularly in colorectal cancers and cancer cell lines[1,3].

In a recent study, using a bacterial fusion protein encoded by CD44 variant exons 8–10 (CD44v8–10), a monoclonal antibody (mAb) 44–1V was established[4]. In an immunohistochemical study, it was shown that the reactivity of colorectal cancer tissues with mAb 44–1V correlated strongly with haematogenous metastasis[5]. The authors now report that the serum concentration of CD44v8–10 is raised in patients whose colorectal cancer tissue showed positive immunostaining, suggesting its usefulness as an indicator or predictor of haematogenous metastasis in patients with colorectal cancer.

Materials and methods

Measurement of serum level of CD44v8–10

Sera obtained from patients with advanced colorectal cancer ($n = 20$) before surgical resection were kept at −80°C before use for determining serum CD44v8–10 levels. An enzyme-linked immunosorbent assay (ELISA) was used to detect the soluble CD44v8–10. Plastic 96-well flat plates coated with antihuman CD44v8–10 monoclonal antibody (mAb 44–1V) were incubated with the samples for 1 h at 37°C. Plates were washed extensively and biotinylated antihuman CD44 standard type immunoglobulin (Ig) mAb (1 mg/ml) was allowed to react with captured CD44v8–10 protein. Streptavidin–biotin–peroxidase (Vector, Burlingame, California, USA) was added to detect bound antihuman CD44 standard type IgG mAb. After washing, 100 μl *o*-phenylenediamine 0·4 mg/ml, hydrogen peroxide 2 μg/ml in citrate buffer (pH 5·0) was added to each well. Finally, the amount of CD44v8–10 protein was determined by measurement of the optical density at 492 nm on a microplate reader.

Immunohistochemical study

Tumour samples obtained from the same 20 patients were fixed in formalin; paraffin-embedded blocks were sliced into 4-μm sections, deparaffinized and endogenous peroxidase activity was eliminated. The sections were stained with mAb 44–1V (1 μg/ml) using an avidin–biotin-peroxidase complex kit (Vector) and 3-3′-diaminobenzidine tetrahydrochloride

Statistical analysis

Statistical analysis was performed by Student's *t* test.

Results

In the immunohistological study, positive staining was intense on the cell membranes of cancer tissue. Adjacent normal colorectal mucosa showed no staining by mAb 44–1V[4,5] except for the base of the crypt. An ELISA system and the immunohistological study were used to explore the relationship between the expression of serum CD44v8–10 concentration and the expression of CD44v8–10 in colorectal cancer tissue. A soluble form of CD44v8–10 protein was present in the serum of patients with colorectal cancers that overexpressed the CD44v8–10 protein in the immunohistochemical assay (*Fig. 1*). However, the level of CD44v8–10 protein in the serum of patients lacking CD44v8–10 expression by immunohistochemistry was low. The mean(s.d.) concentration of soluble CD44v8–10 in the serum of ten patients with positive staining in the colorectal cancers was 1·10(0·20) optical density units, but that in the serum from ten patients whose tumours showed negative staining in colorectal cancers was 0·20(0·12) optical density units ($P < 0{\cdot}01$). Immunoprecipitation with mAb 44–1V revealed the presence of CD44v8–10 protein with a molecular weight of about 130 000 in the serum samples with a raised level of CD44v8–10 (results not shown).

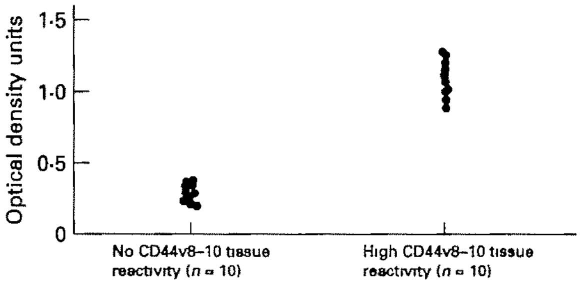

Fig. 1 Serum concentration of protein encoded by CD44 variant exons 8–10 (CD44v8–10) in patients whose colorectal cancer samples exhibited high or no CD44v8–10 tissue reactivity. Mean(s.d.) serum CD44v8–10 concentrations were 1·10(0·20) and 0·20(0·12) optical density units respectively ($P < 0{\cdot}01$, Student's *t* test)

Discussion

The present study has demonstrated the presence of the soluble form of CD44v8–10 protein in the serum of patients with colorectal cancer tissue that overexpressed CD44v8–10 protein in an immunohistological study. However, the serum CD44v8–10 protein level was low in patients with negatively stained tissue. The serum CD44v8–10 level may be determined by the amount of CD44v8–10 protein expressed on each tumour cell.

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Recently, the authors showed that the reactivity of colorectal cancer tissues with mAb 44-1V correlated strongly with haematogenous metastasis in an immunohistological study[5]. Before possible clinical use of this ELISA system as a diagnostic tool or for monitoring for tumour recurrence, a more extensive study will be necessary to determine the limits or conditions of detection. However, this CD44v8-10 ELISA system may be useful to monitor haematogenous metastasis in patients with colorectal cancer.

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Thermogenic, hormonal and metabolic effects of intravenous glucose infusion in human sepsis

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Background Sepsis is associated with alterations in glucose metabolism and the effect of intravenous feeding on energy expenditure is unclear. Many studies of glucose metabolism in humans with sepsis have employed techniques that are not relevant to the practice of intravenous feeding.

Methods The thermogenic, hormonal and metabolic effects of glucose were evaluated in a prospective experimental study of septic ($n = 6$) and non-septic ($n = 6$) subjects, by administering glucose intravenously under conditions and at a rate similar to those used in total parenteral nutrition.

Results Patients with sepsis had a higher fasting metabolic rate than control subjects ($P < 0{\cdot}001$) and a lower fasting respiratory quotient ($P < 0{\cdot}03$). The thermic effect of glucose in both groups was small and not statistically significant (median 3·2 and 0·4 per cent in septic and non-septic subjects respectively, $P > 0{\cdot}1$). Patients with sepsis had an attenuated plasma insulin response to glucose administration compared with control subjects ($P < 0{\cdot}001$) and less marked suppression of plasma fatty acid and glycerol concentrations ($P < 0{\cdot}001$). Glucose administration was not associated with significant changes in plasma catecholamine concentrations in either group of patients.

Conclusion Intravenous infusion of glucose at clinically relevant rates is associated with a negligible thermogenic response, with no activation of the sympathetic nervous system.

The effect of intravenous glucose administration on metabolic rate is unclear. Studies conducted with the glucose clamp technique[1] have suggested that a rise in metabolic rate is invariably associated with glucose and insulin administration[2–5], whereas those in which glucose was administered in isolation have shown trivial increases in metabolic rate and oxygen consumption[6–11]. Similarly, studies using the glucose clamp technique have indicated that activation of the sympathetic nervous system may play an important role in the rise in energy expenditure associated with glucose administration[2–5], but reports of studies in which glucose was given intravenously without exogenous insulin have failed to find evidence of activation of the sympathetic nervous system in healthy subjects[9,11] or in patients with sepsis[6].

The aim of this study was to examine the thermogenic, hormonal and metabolic effects of glucose, given intravenously at a clinically relevant rate to a group of patients with intra-abdominal sepsis, and to compare the responses with those observed in apparently healthy individuals receiving long-term parenteral nutrition. The protocol adopted was chosen to resemble the conditions in which glucose-based total parenteral nutrition (TPN) is given.

Patients and methods

Patients

Twelve subjects requiring TPN gave their informed written consent to take part in the investigation. The protocol had been approved by a local ethics committee and all studies were carried out at Hope Hospital, Salford, UK.

Six patients (four men) presenting with intra-abdominal sepsis made up the sepsis group. The primary cause of sepsis was pancreatitis in one patient, anastomotic dehiscence in two, Crohn's disease in two, and subphrenic abscess associated with perforated duodenal ulcer in one. At the time of study, a sepsis score was calculated for each patient using established methodology[12]. The scoring procedure, which takes into account the site of infection, bacteriology, body temperature, secondary effects (e.g. jaundice) and various haematological and biochemical variables, such as white cell and platelet counts and plasma albumin concentration, revealed a range of sepsis scores from 9 to 18, indicative of moderately severe sepsis. At the time of study, either patients had undrained sepsis or a septic focus had been drained in the previous 72 h.

The no-sepsis (control) group comprised six apparently healthy individuals (five men) who required TPN for previous intestinal disease (Crohn's disease in two, volvulus in three, infarction in one). All patients had been fed intravenously for at least 10 months and had been weight stable for at least 2 months before the study. At the time of the study, no sepsis or other inflammatory processes were clinically evident and hence all the control subjects had sepsis scores of zero.

All subjects received TPN for at least 2 weeks before the study. This treatment comprised a cyclical nocturnal TPN regimen (given over 14 h on at least four nights per week) consisting of a 3-litre solution (9·0 MJ, 2150 kcal) containing 500 g dextrose, 9·1 g nitrogen as amino acids with added electrolytes, vitamins, trace elements and heparin made up in 0·9 per cent sodium chloride. Lipid solution (20 per cent, 4·2 MJ, 1000 kcal) was provided one or two nights per week. Further details of the subjects are provided in *Table 1*.

Protocol

Before investigation, subjects were deprived of enteral and parenteral nutrition and abstained from nicotine, caffeine and alcohol for 10 h. In addition, no patient received steroids, β-blockers, thyroid or other medication known to affect metabolic rate for at least 3 months before the study.

Body mass and height were recorded on the morning of the study. Harpenden calipers (Holtain, Crymych, Pembrokeshire, UK) were used to measure skinfold thickness at four anatomical sites for estimation of percentage body fat (from the tables of

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Table 1 Details of the 12 patients studied

Subject	Age (years)	Height (cm)	Weight (kg)	Body fat (kg)	Fat-free mass (kg)	Nitrogen output (g per 24 h)	Sepsis score
No sepsis							
1	42	186	66·5	13·0	53·5	4·8	0
2	51	178	75·8	24·8	51·0	3·6	0
3	52	177	67·0	13·9	53·1	5·2	0
4	27	177	70·0	9·0	61·0	9·8	0
5	22	169	61·5	5·0	56·5	6·3	0
6	34	166	40·4	6·9	33·5	4·9	0
Median	38	177	66·8	11·0	53·3	5·0	
Sepsis							
1	45	174	75·3	21·2	54·1	12·5	15
2	23	182	89·7	11·6	78·1	15·6	12
3	59	174	50·5	7·9	42·6	10·2	9
4	68	181	52·7	6·6	46·1	7·8	18
5	29	165	64·4	23·0	41·4	16·7	13
6	37	170	66·4	18·6	47·8	13·8	11
Median	41	174	65·4	15·1	47·0	13·2*	12·5

*$P < 0·005$ *versus* control (Mann–Whitney U test)

Durnin and Womersley[13]) Body fat and fat-free mass (FFM) were calculated accordingly. A cannula was then inserted into an antecubital vein for blood sampling, and the subject was allowed to rest for 20 min in a supine position before proceeding. After the rest period, indirect calorimetry (Deltatrac; Datex, Helsinki, Finland) was started and continued throughout the 3-h study. The calorimeter uses a gas dilution canopy system for the measurement of V_{O_2} (oxygen consumption) and V_{CO_2} (carbon dioxide excretion) as described elsewhere[14]. Readings for V_{O_2} and V_{CO_2} were averaged every 6 min throughout the study period The calorimeter was calibrated before and after each study with the manufacturer's recommended gases, having previously been validated by alcohol combustion and shown to deliver values of V_{O_2} and V_{CO_2} within 98 per cent of those predicted. Baseline measurements were taken for 1 h before 60 g glucose (Steriflex; Boots Hospital Products, Nottingham, UK) was infused for 2 h (started at time zero) at a rate of 150 ml/h (471·2 kJ/h) through the subject's central venous cannula. Venous blood samples were withdrawn 15 min before and at 15-min intervals from the start of the glucose infusion Urine and fistula outputs were collected during the 24-h period after the experiment and the nitrogen content of all specimens was determined by automated Kjeldahl equipment (Foss Electric, Copenhagen, Denmark) for estimation of total nitrogen output. No corrections were made for insensible losses of nitrogen. Urinary nitrogen excretion was used, together with gas exchange data, for the calculation of resting energy expenditure (REE), using the formula of de Weir[15].

Plasma glucose, lactate, free fatty acid (FFA) and glycerol concentrations were measured by an automated (Cobas Bio; Roche, Welwyn Garden City, UK) enzymatic fluorometric assay. Radioimmunoassay techniques were used for the determination of plasma concentrations of insulin and glucagon (kit; Novo Biolabs, Bagsvaerd, Denmark). Adrenaline and noradrenaline were assayed by high-performance liquid chromatography, with electrochemical detection as described previously[16]. Blood culture, haematological count and other investigations required for calculation of the sepsis score were conducted by the microbiology, chemical pathology and haematology departments of the hospital.

Calculations and statistical analysis

FFM is known to be the principal site of thermogenesis and thus oxygen uptake was expressed in terms of FFM to negate any effects that differences in body composition may have produced. The areas under the baseline (− 54 to 0 min) and response (100–120 min) curves for REE and respiratory quotient (RQ) were measured using the trapezoid method. After extrapolating the baseline area to 20 min the baseline value was subtracted from the area under the response curve between 100 and 120 min inclusive to determine the nutrient-induced response In addition, the thermic effect of glucose in each patient group was calculated by subtracting the energy expended during the baseline period (corrected to the time period of the infusion) from the total energy expended during the infusion and expressing the result as a percentage of the total calories provided during each infusion.

Changes in REE and RQ within and between groups were analysed statistically using a paired and unpaired Student's t test respectively, and the thermic effect of glucose in septic and non-septic individuals was compared with the Mann–Whitney U test. Biochemical responses were analysed using repeated-measures analysis of variance. In the case of insulin and catecholamine results, log values were analysed because these data have previously been shown to be log-normally distributed[17,18]. For both groups of patients the statistical significance of the change in each biochemical variable with time was assessed by calculating the time effect and the difference between the sepsis and control groups examined by calculating sepsis–time interaction, as described previously[11]. Degrees of freedom within and between groups are indicated as subscripts to the relevant F values All statistical analyses were performed with Statistical Package for the Social Sciences computer software (SPSS UK, Chertsey, UK). The level of statistical significance was taken as $P < 0·05$.

Results

The effect of glucose infusion on REE is shown in *Fig. 1*. Baseline REE was significantly higher in patients with sepsis than in controls ($t = 4·48$, 10 d.f., $P < 0·001$) and remained so throughout the period of glucose infusion ($t = 3·38$, 10 d.f., $P < 0·01$). There was no significant difference between the area under the curve for the last 20 min of the glucose infusion and the baseline (corrected to 20 min) in either septic ($t = 1·52$, 5 d.f., $P > 0·1$) or control ($t = 1·52$, 5 d.f., $P > 0·1$) subjects. No statistically significant thermic effect of glucose was therefore observed in either group of patients (*Table 2*).

The RQ values of patients with sepsis began lower and ended lower (*Fig. 2*). The baseline value of RQ was significantly lower in patients with sepsis ($t = 3·1$, 10 d.f., $P < 0·03$). The area under the curve for the infusion period was lower for patients with sepsis, but this difference was not statistically significant ($t = 1·8$, 10 d.f.,

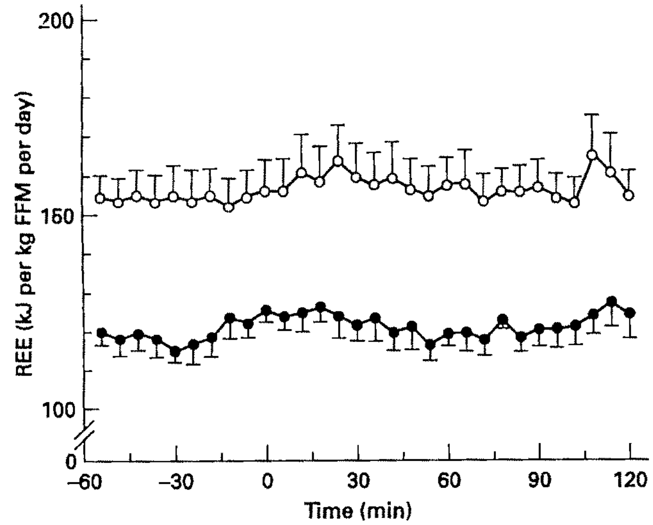

Fig. 1 Resting energy expenditure (REE) before and during glucose infusion (started at time zero) in six patients with sepsis (○) and six control subjects (●). Values are mean(s.e.m.). FFM, fat-free mass

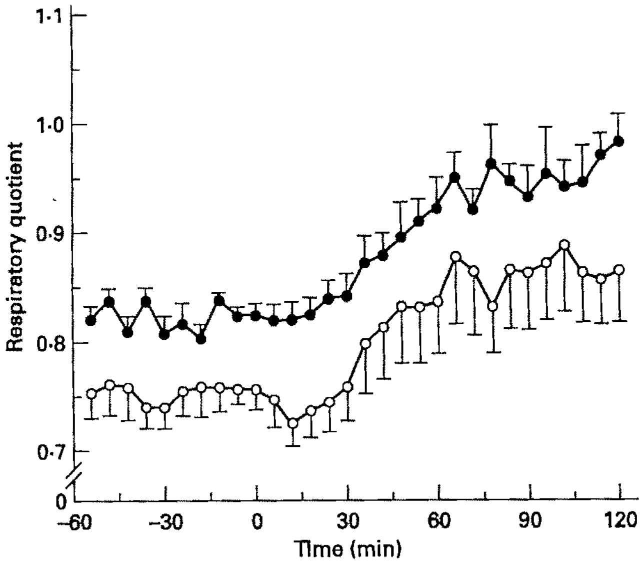

Fig. 2 Respiratory quotient before and during glucose infusion (started at time zero) in six patients with sepsis (○) and six control subjects (●) Values are mean(s.e m.)

$P=0{\cdot}09$). In both groups of patients, the RQ rose significantly during glucose infusion ($t=5{\cdot}9$, 5 d.f., $P<0{\cdot}01$ and $t=4{\cdot}0$, 5 d.f., $P=0{\cdot}01$ for non-septic and septic patients respectively).

Fasting plasma glucose concentrations were similar and there were similar rises (*Fig. 3d*) in plasma glucose level associated with glucose infusion in patients with and without sepsis (sepsis–time interaction $F_{9,110}=0{\cdot}92$, $P>0{\cdot}5$). Similar results (*Fig. 3c*) were noted for plasma lactate concentration (sepsis–time interaction $F_{9,110}=0{\cdot}5$, $P>0{\cdot}8$).

Fasting plasma glycerol and FFA (*Fig 3a* and *b*) concentrations were also similar in those with and without sepsis, and fell significantly in response to glucose administration in both septic (time effect $F_9=8{\cdot}2$, $P<0{\cdot}001$ and $F_9=12{\cdot}0$, $P<0{\cdot}001$ for glycerol and FFAs respectively) and non-septic (time effect $F_9=19{\cdot}1$, $P<0{\cdot}001$ and $F_9=32{\cdot}0$, $P<0{\cdot}001$ for glycerol and FFAs respectively) subjects. Glucose infusion resulted in a greater reduction in plasma glycerol and FFA concentration in control subjects than in patients with sepsis (sepsis–time interaction $F_{9,110}=2{\cdot}2$, $P=0{\cdot}03$ and $F_{9,110}=3{\cdot}8$, $P<0{\cdot}001$ for glycerol and FFAs respectively).

Plasma insulin levels (*Fig. 4c*) rose smoothly in both septic and non-septic patients in response to glucose, but the response was dampened significantly in those with sepsis (sepsis–time interaction $F_{9,110}=6{\cdot}1$, $P<0{\cdot}001$). Plasma adrenaline levels (*Fig. 4b*) were higher throughout the period of study in patients with sepsis compared with controls. There was no significant difference when the responses of septic and control patients were compared (sepsis–time interaction $F_{9,110}=1{\cdot}3$, $P>0{\cdot}3$). Plasma noradrenaline concentrations were not significantly higher in patients with sepsis (*Fig. 4a*). Noradrenaline

Table 2 Energy expenditure and thermic effect of glucose in patients with sepsis and control subjects

	Energy expended during baseline (60 min) period (kJ)	Energy expended during infusion (120 min) period (kJ)	Change in energy expended during infusion (kJ)	Energy infused (kJ)	Thermic effect (%)
Control subjects					
1	485·1	550·2	65·1	942·5	6·9
2	543·5	538·0	−5·5	942·5	−0·6
3	504·0	474·6	−29·4	942·5	−3·1
4	628·7	613·2	−15·5	942·5	−1·6
5	531·3	546·4	15·1	942·5	1·6
6	368·8	383·0	14·2	942·5	1·5
Median	517·4	542·2	24·8		0·4
Patients with sepsis					
1	543·9	551·9	8·0	942·5	0·8
2	706·0	742·1	36·1	942·5	3·8
3	483·8	487·6	3·8	942·5	0·4
4	678·7	704·3	25·6	942·5	2·7
5	1092·0	1168·9	76·9	942·5	8·2
6	521·2	515·8	−5·4	942·5	−0·6
Median	611·5	628·3	16·8		3·2

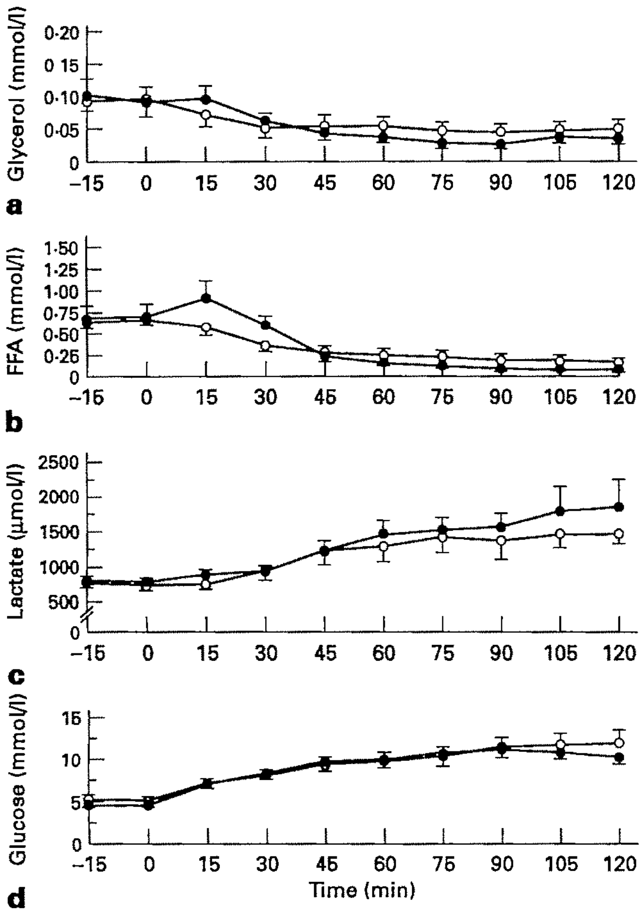

Fig. 3 a Glycerol, b free fatty acid (FFA), c lactate and d glucose concentrations before and during glucose infusion (started at time zero) in six patients with sepsis (○) and six control subjects (●). Values are mean(s.e.m.)

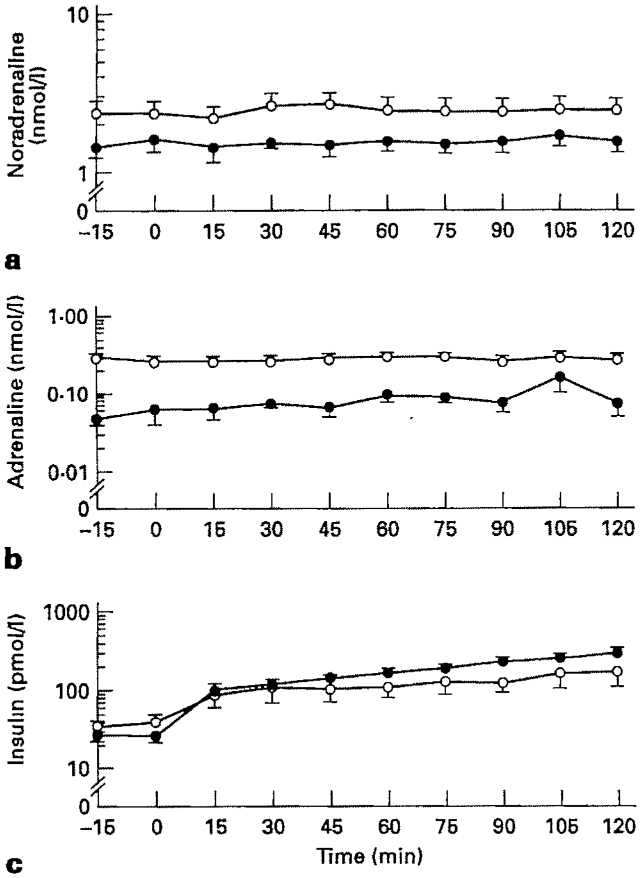

Fig. 4 Plasma concentrations of a noradrenaline, b adrenaline and c insulin before and during glucose infusion (started at time zero) in six patients with sepsis (○) and six control subjects (●). Values are mean(s.e.m.)

concentration did not change significantly with time in either group (time effect $F_9=0\cdot6$, $P>0\cdot5$ in controls and $F_9=0\cdot5$, $P>0\cdot5$ in patients with sepsis).

Discussion

This study confirms that patients with intra-abdominal sepsis have a fasting REE almost 30 per cent greater than that in control subjects, whereas fasting RQ was significantly lower. Previous studies of healthy and malnourished individuals have indicated the thermic effect of glucose to be 5–10 per cent of the calories administered[2–5], whereas no significant rises in REE were observed in the present study with glucose administration in septic or control subjects. Earlier reports were of studies in which combined infusion of glucose and insulin was used to establish stable conditions of glycaemia and hyperinsulinaemia. These studies were frequently associated with unphysiological rates of glucose storage, far in excess of those observed during parenteral nutrition, whereas the conditions employed in the present study resembled more closely those in which patients are fed parenterally. This difference may explain in part the present findings, as a significant proportion of the increase in energy expenditure associated with glucose administration has been attributed to the energetic costs of glucose storage (obligatory thermogenesis[19]). Other studies that have examined the thermic effect of glucose in conditions closely resembling parenteral nutrition have also reported low thermic effects[7–11]. A further explanation for the failure to observe significant glucose-induced thermogenesis in the present study may relate to the duration of glucose infusion. During the 2-h period of glucose administration, a significant proportion of the infused glucose must have been consumed in filling the glucose space. Using previous estimates of 250 ml/kg[20], the glucose space would account for a median (range) 27·2 (15·2–24·9) per cent and 36·0 (18·8–39·3) per cent of glucose administered to control and septic subjects respectively. This glucose would have exerted little or no metabolic effect. However, by 90 min, no further increment in plasma glucose concentration was observed in either group and the failure of REE to increase after this time implies an alternative explanation. In addition, studies of glucose infusion alone over longer periods have failed to show thermic effects as large as those associated with combined glucose–insulin infusions[7,8]. It is thus unlikely that prolongation of the glucose infusion beyond the 2 h used in the present study would have produced different results.

Glucose administration in patients with sepsis has been shown to lead to increased REE and urinary catecholamine excretion[21]. In the present study, the trivial rise in REE associated with the administration of glucose to patients with and without sepsis was not associated with a rise in plasma catecholamine concentration. The apparent discrepancy between these results and those of earlier reports may relate to differences in the manner in which glucose was administered. In particular, earlier studies have employed bolus administration of glucose[22], which may have produced a different pattern of insulin response to that associated with continuous infusion. In addition, insulin itself is believed to stimulate sympathetic nervous system activity[23]. In the study reported by Askanazi *et al.*[21], a complete TPN regimen was administered and the increase in urinary noradrenaline excretion was observed after a period of at least 3 days of nutrition, suggesting that the catecholamine response may be chronic rather than acute. Recent studies have indicated plasma catecholamine concentration to be an inaccurate reflection of sympathetic nervous system activity in sepsis[24], and kinetic measurements of catecholamine turnover in response to glucose administration are required to clarify this finding.

Fasting plasma insulin concentrations were similar in the two groups of patients but the insulin response to glucose administration appeared to be dampened in sepsis. The significance of this finding is unclear because controversy exists regarding the effect of sepsis and injury on the interrelationship between plasma glucose and insulin concentrations[6,25,26]. As insulin clearance is altered in sepsis and has seldom been measured[27], the relationship between plasma concentration of insulin and the pancreatic secretory response to infused glucose is unclear. The combination of a dampened plasma insulin response and a normal plasma glucose profile after glucose administration does, however, imply the absence of insulin resistance. In the present study insulin sensitivity was not measured, but the finding of a reduced rate of glucose oxidation and a failure of plasma FFA and glycerol concentrations to fall to the same level in septic and non-septic patients implies continuing lipolysis and utilization of lipid as fuel substrate. While this has previously been equated with insulin resistance, the presence of a reduced plasma insulin level in patients with sepsis implies an alternative mechanism. The plasma glucose response may reflect insulin-independent glucose uptake, which has been reported in experimental models of sepsis[28] and may explain the lack of hyperglycaemia.

In summary, the administration of glucose to patients with sepsis in conditions resembling TPN is associated neither with increments of REE nor with clear evidence of sympathetic nervous stimulation. Although patients with sepsis had a similar plasma glucose response to that in control subjects, the plasma insulin response was dampened and this was associated with a reduction in glucose oxidation and continued utilization of lipid as fuel substrate. The thermic effect of glucose may not be of major practical significance when assessing the energy requirements of parenterally fed patients with intra-abdominal sepsis.

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Influence of direction of view, target-to-endoscope distance and manipulation angle on endoscopic knot tying

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Introduction The aim of the study was to investigate the influence of (1) the direction of view of the endoscope, (2) the endoscope-to-task distance and (3) the manipulation angle between the instruments on intracorporeal endoscopic knotting.

Methods Rigid endoscopes (0°, 30° and 45°) were introduced with the objective set at distances of 50, 75, 100, 125 and 150 mm from the task. Needle holders were inserted to make 30°, 60° and 90° manipulation angles. The execution time and knot quality parameters of 2700 knots performed by ten surgeons were obtained.

Results There was no significant difference in the execution time or parameters of knot quality with different endoscopes. The longest execution time (median 95 s, $P<0{\cdot}0001$) and the lowest performance quality score (20·61, $P<0{\cdot}001$) were observed at a distance of 50 mm when compared to other distances. A 60° manipulation angle had a shorter execution time (median 71 s, $P<0{\cdot}0001$) and a higher performance quality score (26·84, $P<0{\cdot}0001$) than either 30° or 90° manipulation angles.

Conclusion The direction of view of the endoscope had no significant effect on intracorporeal knotting if the optical axis subtended the same angle with the task surface. The optimal ergonomic conditions include an endoscope-to-target distance of 75–150 mm and a manipulation angle of 60°.

The basic optics of the modern rigid endoscope consists of an objective lens, a relay system based on the Hopkins rod-lens system[1,2] and an eyepiece lens with distal illumination by means of fibreoptic light bundles. The direction of view of the endoscope can be forward viewing or at varying degrees from the horizontal. To obtain a forward–oblique direction of view, for example 30° or 45°, the optical axis is deflected at the distal end of the endoscope by light-deflecting prisms incorporated as part of the objective[1]. Direction of view of the endoscope is defined as the angle between the centre of the visual field (optical axis) and the longitudinal axis of the endoscope. Deflection of the optical axis by these prisms enables the view to be changed by rotation of the endoscope around its longitudinal axis. This undoubted advantage of forward–oblique endoscopes is offset by the reduced light transmission compared with that of forward-viewing systems.

In addition to the direction of view, other important characteristics of rigid endoscopes include the viewing angle and the field of view. The viewing angle refers to the angle formed by the two outer visual limits and determines the diameter of the field of view and the size of the objects seen. The field of view describes the area inspected by the tip of the endoscope. At a given distance from the lens, the larger the field of view, the greater the area that can be observed[3].

Most of the reported research on video-endoscopes has been focused on the assessment of optical characteristics[1,4–8], with little information on the effect of the optical design on surgical task performance. The aim of the study was to investigate the influence of (1) the direction of view of the endoscope, (2) the distance between the task and the objective of the endoscope and (3) the manipulation angle between the instruments on surgical task performance.

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Materials and methods

Task

The standardized task consisted of tying an intracorporeal surgeon's knot with 2/0 silk of 200 mm inserted through a block of light yellow foam. The foam block was 25×75×155 mm A longitudinal groove in the middle of the back of the foam housed a rubber tube The foam was mounted with Velcro on the oblique surface of a right-angled block of wood. Two silk threads were passed round the rubber tube from the front, one at each end of the block, at a distance of 30 mm from the middle of the foam. At each site, the thread was passed from the exact points as marked on the foam with a 10-mm distance between the entry and exit points and with equal lengths of thread outside the foam on either side. The assembled task rig was stabilized in place inside a box (450×350×250 mm). The base, sides and back were made of wood whereas the front and top were of brown cardboard attached to the wood with Velcro. Strips of neoprene were sutured to the cardboard into which trocars were inserted to allow manoeuvrability of the instrument whilst retaining the port positions.

Equipment

Endoscopes. Forward-viewing 0°, forward–oblique 30° and 45° Hopkin's I endoscopes of 10-mm diameter and 33-cm length (Karl Storz, Tuttlingen, Germany) were used throughout the experiment.

Light sources. Storz coldlight fountain 450-V light sources were used only during the first 150 h of their lifespan (about 250 h) as significant deterioration of light output occurs during the last 10 per cent of the bulb's lifespan The light source was connected to all the endoscopes using 495NL fibreoptic light cables of 3·5-mm diameter and 180-cm length (Karl Storz).

Camera and monitor. The Storz Endovision 9050-PB single-chip camera (Karl Storz) and Sony PVM-1443MD high-resolution (more than 600 TV lines) monitors (Sony, Tokyo, Japan) were used for the experiments. The monitor was placed directly facing the surgeon at a distance of 1 m with the centre of the monitor at eye level.

Needle holders, trocars and cannulas. Intracorporeal knot tying was performed using a pair of 26173SK Cuschieri needle drivers (Karl Storz). The instruments were inserted through reusable 11- and 5·5-mm ports (Karl Storz).

Experimental procedures

Forward-viewing 0° and forward-oblique 30° and 45° endoscopes were introduced through the front and top cardboard via 11-mm ports such that the optical axis of the endoscope was perpendicular to the target surface at the knot location with the objective at distances of 50, 75, 100, 125 and 150 mm from the knot (*Fig. 1*)

The needle drivers were inserted through the top cardboard via 5·5-mm ports perpendicular to the plane of the oblique surface of the foam block, making 30°, 60° and 90° manipulation angles between the needle holders, 15°, 30° and 45° angles between the axis of the instrument and the optical axis of the endoscope (azimuth angle), and a 60° elevation angle between the instrument and the horizontal plane (*Fig. 2*). A computer-aided design program (Autocad; Autodesk, Guildford, UK) was used for these measurements.

Ten surgeons of variable clinical experience who had received training in knot tying during the advanced laparoscopic courses in Dundee participated in the study. Group 1 (five surgeons) performed only basic laparoscopic operations (diagnostic laparoscopy and laparoscopic cholecystectomy) whereas group 2 had experience in advanced laparoscopic procedures (fundoplication, oesophagectomy and colectomy). All surgeons had corrected eyesight. The combination of endoscopes and instruments produced 45 positions. Each surgeon performed six knots in each position. The study was designed so that each surgeon completed the study in three equal practice runs Each run consisted of two knots in each of the 45 positions and the run was completed in three sessions. The sequence of positions in each practice run was randomized.

After tying the intracorporeal surgeon's knot, the thread loop round the tube was divided at the opposite pole of the knot. All the knots performed by each operator were numbered and coded for the operator and position. The time taken to execute each knot was measured from the moment the operator grasped the handles of the needle holders until the instruments were released on completion of each intracorporeal knot.

Knot testing apparatus

Testing was performed with an Instron tensiometer (model 1026; Instron, High Wycombe, UK). Knots were distracted between the clamps of the tensiometer and signals from the load cell (maximum 20 kg) were fed to a signal conditioning unit which provided a gain of 100 and a filter to remove the high frequency noise The modified signal was recorded by an analogue to digital conversion card with a sampling frequency of 25 Hz (Advantech PCL-812PG, Roldec System, Wolverhampton, UK) inserted in the computer recording system. A software program (Snapshot, HEM Data, Southfield, Michigan, USA) controlled the conversion card and displayed the load cell waveform A data analysis program (written in Matlab; The Math Work Incorporated, Natick, Massachusetts, USA) was used to smooth the data (by digital filtering), to remove zero offsets, to apply the load cell calibration factor, to synchronize each record using a digital trigger, to derive extension correlates to the force data and to calculate knot quality parameters The extension values were obtained from the tensiometer jaw separation speed (50 mm/min) and the sampling frequency. The two ends of the divided loop of the knot were inserted between the jaws of the clamps and distracted by the tensiometer.

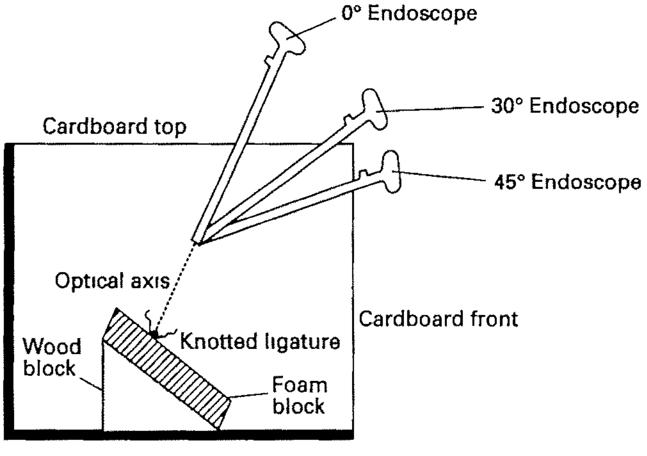

Fig. 1 Diagram of the experimental apparatus with the endoscopes introduced so that the optical axis is perpendicular to the target surface

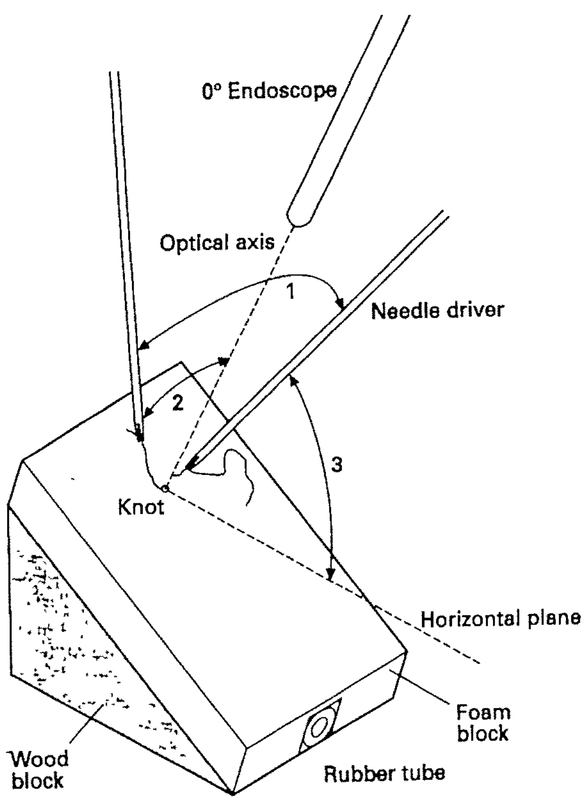

Fig. 2 Diagram of the task rig showing the manipulation angle (1), azimuth angle (2) and elevation angle (3) of the instruments

Performance and knot quality parameters[9]

An evaluation of the curves was conducted by Matlab programs, and this yielded a number of output parameters. The maximum force necessary to break the knot was taken as the breaking force and the slipping force required to undo the knot (without breakage of the silk) was defined as the mean force of the plateau of the curve. The integrated force of the curve slope (N) and the work done (N m) were measured between 0·672 and 2·016 mm on the x coordinate. The curves start to rise from the common intersection of a point corresponding to 0·672 mm, whereas the value on the curve corresponding to 2·016 mm on the x coordinate identifies the point on the curve at which the breaking force of untied ligature (2/0 silk) is reached (*Fig 3*). The breaking or slipping force reflects the strength of the knot, and measurement of the slope of the curve reflects the degree of

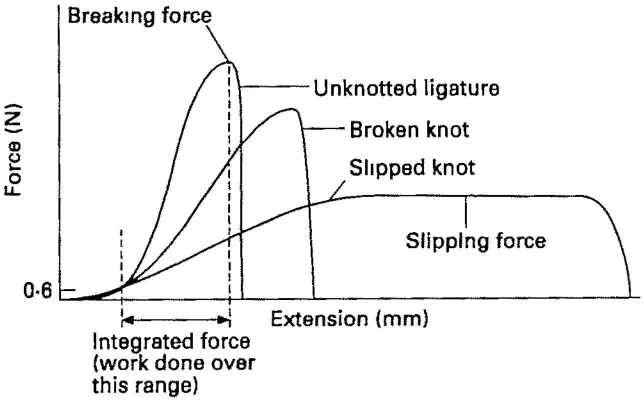

Fig. 3 Force–extension curves of unknotted ligature, broken knot and slipped knot. The curves are aligned at 0·6 N

tightening. A knot quality score (KQS) was derived as follows:

$$\mathrm{KQS} = \frac{\text{Breaking or slipping force of knot}}{\text{Breaking force of thread}} \times \frac{\text{Integrated force of the slope of knot}}{\text{Integrated force of the slope of thread}} \times 100$$

The time of execution of the task was used as a measure of task efficiency. To relate the quality of the knot to task efficiency, a performance quality score (PQS) was obtained:

$$\text{Performance quality score} = \frac{\text{Knot quality score}}{\text{Execution time score}}$$

The execution time score relates the execution time for each knot to a norm-referenced execution time which, in the present study, was defined as the mean execution time for the entire population.

Statistical analysis

The data for execution time, force, work done, KQS and PQS were not normally distributed and could not be normalized by any method of transformation. Therefore, non-parametric tests such as Kruskal–Wallis one-way analysis of variance and the Mann–Whitney U test were used, as appropriate. Significance was set at the 5 per cent level.

Results

Direction of view of the endoscope

Nine hundred knots were tied with each endoscope. The number of slipped knots was 141, 133 and 138 on using the forward-viewing, 30° and 45° endoscopes respectively. Logistic regression showed that the number of slipped knots was not significantly different between endoscopes ($P = 0.84$). *Table 1* shows the median (interquartile range (i.q.r.)) of the execution time and parameters of knot analysis, with no significant difference between endoscopes. Furthermore, the difference between the endoscopes was not significant at any particular distance or with any manipulation angle.

Distance of the endoscope from the task

Some 540 knots were tied at each distance. The number of slipped knots was 88, 74, 88, 77 and 85 at distances of 50, 75, 100, 125 and 150 mm respectively between the task and the objective of the endoscope. Logistic regression showed that the distance did not influence the number of slipped knots ($P = 0.91$).

Table 2 shows the median (i.q.r.) of the execution time and parameters of knot analysis for different distances. The worst performance was observed when intracorporeal knots were tied at an endoscope-to-task distance of 50 mm, which resulted in the longest execution time and

Table 1 Effect of the direction of view of the endoscope on knot tying

	Endoscope				
	0°	30°	45°	P*	χ^2
Time (s)	83 (37)	83 (37)	83 (37)	0·50	1·38
Force (N)	23·36 (4·38)	23·41 (4·51)	23·26 (4·28)	0·88	0·26
Work (N m)	0·019 (0·011)	0·019 (0·012)	0·019 (0·011)	0·96	0·08
Knot quality score (%)	21·79 (17·09)	22 09 (17·67)	22·08 (16·34)	0·72	0·65
Performance quality score	22·96 (19·64)	23·59 (21·63)	22·31 (19·78)	0·42	1·74

Values are median (interquartile range). *Kruskal–Wallis one-way analysis of variance (2 d.f.)

Table 2 Effect of the distance of the endoscope from the task on knot tying

	Distance (mm)						
	50	75	100	125	150	P*	χ^2
Time (s)	95 (41)	80 (35)	80 (33)	80 (32)	80 (38)	<0·0001	88·17
Force (N)	23·41 (4·31)	23·51 (4·09)	23·21 (5·05)	23·16 (4·29)	23·44 (4·49)	0·56	3·00
Work (N m)	0·019 (0·012)	0·019 (0·012)	0·019 (0·010)	0·019 (0·011)	0·019 (0·011)	0·79	1·69
Knot quality score (%)	22·17 (17·88)	22·54 (17·86)	22·48 (15·72)	21·18 (16·37)	21·56 (16·90)	0·81	1·58
Performance quality score	20·61 (18·43)	24 23 (20·33)	24·60 (21·57)	22·46 (20·29)	22·98 (20·63)	<0·0001	29·82

Values are median (interquartile range). *Kruskal–Wallis one-way analysis of variance (4 d.f.)

the lowest PQS. Differences in the execution time and the PQS between 50 mm and other working distances studied were highly significant ($P<0{\cdot}0001$ and $P<0{\cdot}001$ respectively, Mann–Whitney *U* test). No significant differences were observed between the working distances and the force, work done or KQS.

Manipulation angle

Nine hundred knots were tied with each angle. The numbers of slipped knots were 138, 120 and 154 knots with 30°, 60° and 90° manipulation angles respectively. The manipulation angle did not have any significant effect on the number of slipped knots ($P=0{\cdot}29$).

Table 3 shows the median (i.q.r.) of parameters of knot analysis for each angle. A significant difference in the execution time between different angles was observed, with the 60° angle being the best ($P<0{\cdot}0001$, Mann–Whitney *U* test). Both 60° and 90° manipulation angles had a significantly higher force than the 30° angle ($P<0{\cdot}005$ and $P<0{\cdot}05$ respectively), whereas both 60° and 30° angles had significantly higher work done than the 90° angle ($P<0{\cdot}005$ and $P<0{\cdot}0001$ respectively). The PQS with the 60° angle was significantly higher than that obtained using 30° or 90° manipulation angles ($P<0{\cdot}0001$).

Surgeon

The number of slipped knots ranged between seven and 99 knots per 270 knots tied by each surgeon. Logistic regression showed that the number of slipped knots was significantly different between surgeons ($P<0{\cdot}001$). *Table 4* shows the median (i.q.r.) of the execution time and parameters of knot analysis for each surgeon. Knot quality and task efficiency showed significant differences between surgeons ($P<0{\cdot}0001$). In addition, group 2 (experienced laparoscopic surgeons) had a significantly higher PQS

Table 3 Effect of manipulation angle on endoscopic knot tying

	Manipulation angle				
	30°	60°	90°	P*	χ^2
Time (s)	95 (42)	71 (31)	85 (33)	<0·0001	336·02
Force (N)	23·02 (4·40)	23·47 (4·00)	23·53 (4·68)	<0·01	9·71
Work (N m)	0·020 (0·012)	0·019 (0·011)	0·018 (0·011)	<0·0001	21·99
Knot quality score (%)	22·84 (17·04)	22·56 (15·97)	20·48 (17·45)	<0·005	11·03
Performance quality score	21·05 (18·44)	26·84 (20·65)	21·53 (19·39)	<0·0001	89·53

Values are median (interquartile range). *Kruskal–Wallis one-way analysis of variance (2 d.f.)

Table 4 Effect of the surgeon on endoscopic knot tying

	Surgeon no											
	1	2	3	4	5	6	7	8	9	10	P*	χ^2
Time (s)	105 (41)	62 (29)	95 (36)	66 (24)	80 (26)	80 (32)	97 (24)	67 (34)	84 (28)	81 (29)	<0·0001	625·04
Force (N)	24·65 (3·68)	21·83 (4·26)	20·94 (13·01)	23·88 (3·81)	24·12 (3·12)	21·99 (5·74)	24·94 (3·12)	22·66 (5·42)	25·07 (3·99)	22·54 (3·54)	<0·0001	471·36
Work (N m)	0·017 (0·007)	0·013 (0·007)	0·013 (0·008)	0·016 (0·008)	0·028 (0·008)	0·023 (0·010)	0·025 (0·010)	0·017 (0·010)	0·024 (0·008)	0·018 (0·008)	<0·0001	1040·95
Knot quality score (%)	21·44 (11·32)	14·29 (10·35)	12·49 (12·55)	18·03 (11·71)	35·15 (12·27)	24·97 (18·42)	31·50 (12·38)	18·89 (16·60)	29·93 (12·42)	20·23 (11·38)	<0·0001	924·67
Performance quality score	17·29 (11·33)	17·95 (14·89)	11·33 (11·89)	22·32 (19·42)	36·77 (19·36)	27·39 (23·52)	28·12 (14·44)	22·21 (21·95)	31·16 (19·45)	21·42 (15·49)	<0·0001	615·41

Values are median (interquartile range) *Kruskal–Wallis one-way analysis of variance (9 d f)

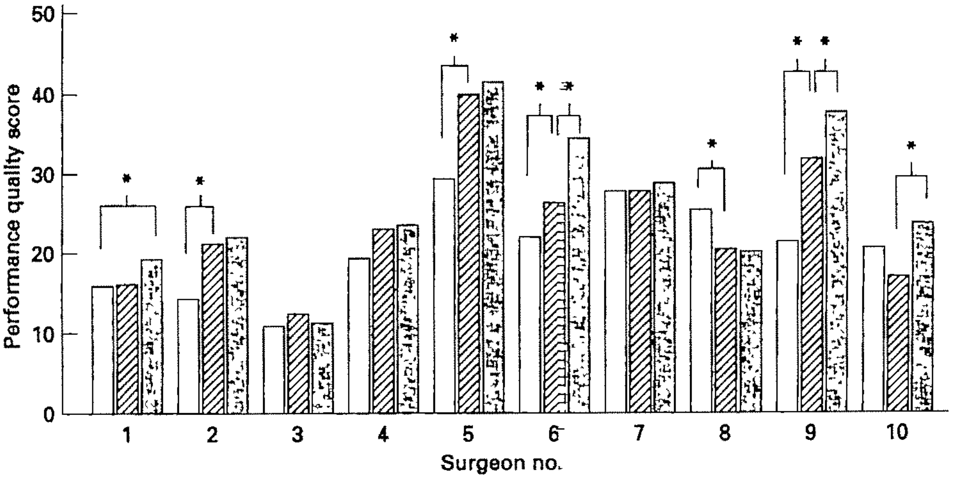

Fig. 4 Effect of practice on performance quality score: □, first run; ▨, second run; □, third run. *$P<0{\cdot}05$ (Mann–Whitney *U* test)

(median 23·93 (i.q.r. 18·38)) than group 1 (basic laparoscopic surgeons) (median 21·61 (i.q.r. 22·36)), $P<0{\cdot}005$. No significant difference was observed in any of the knot parameters (force, work done and KQS) between the first and subsequent knots within each practice run ($P=0{\cdot}1$). While practice did not improve the performance of four surgeons, six showed a significant improvement between runs (*Fig. 4*).

Discussion

There was no significant difference in task efficiency or knot quality between endoscopes of different directions of view when the optical axis of the endoscope was set perpendicular to the task. It is important to emphasize, however, that this study was designed to investigate the effect of the direction of view of the endoscope with the optical axis subtending the same angle to the target surface. The operative field of forward-viewing endoscopes is constant irrespective of the axis of rotation of the endoscope, whereas the visual field changes when the forward–oblique endoscope is rotated. The accessibility and anatomy of the operative field and the complexity of the procedure dictate the endoscope required. From the practical standpoint, more experience is needed in driving oblique-viewing endoscopes.

The distance between the objective and the task determines three important factors: the size of the field of view, and the magnification and intensity of illumination. The field of view becomes smaller as the distance between the endoscope and the task decreases. In the case of intracorporeal knotting at close distances, the operator has to manipulate the ligature outside the field of view and then bring the thread into the field to perform the component wraps. This accounts for the longer execution time at the 50-mm distance. The magnification of the operative target is inversely proportional to the distance between the end of the telescope and the operative field. On the other hand, magnification increases the apparent speed of movement and the operator has to bring the movement in line with the degree of magnification, i.e. speed of movement is decreased as the magnification is increased. The amount of light gathered by the endoscope is higher at close distances. However, glare may degrade image quality, although this factor was not experienced in the present study. The intensity of illumination produced by oblique-viewing endoscopes is less than that of forward-viewing types.

Instrument clashing is another important factor that degrades task performance. Surgeons experienced clashing of needle holders with the endoscope at the 50-mm distance. Reduction of task performance at 50 mm is thus explained by a combination of instrument clashing, reduced field of view and increased magnification. By contrast, with other distances studied the illumination and size of the field of view were sufficient for adequate execution.

All surgeons had the shortest execution time with the 60° manipulation angle and the longest time with the 30° angle. In addition, the 60° manipulation angle carried the highest knot strength. Within the experimental set-up used in this investigation, a 60° manipulation angle had the best performance with all the endoscopes and at any distance. This study showed that there was no interaction between the manipulation angles of instruments and the distance between the endoscope and the task or the direction of view of the endoscope when the instrument and the optical axis of the endoscope were in the same plane.

In addition to the difference in individuals' performance, the effect of practice was different between trainees. The performance of four surgeons did not improve, whereas that of six surgeons improved significantly. Two of the four who did not improve were experienced laparoscopic surgeons. These surgeons had reached the maximum skill commensurate with their innate ability. Surgeons who had the highest and lowest PQS were from the less experienced group. While the surgeon who had the highest PQS continued to improve, the surgeon with the lowest score failed to show any improvement. This contrast in individual performance demonstrates the need for selection of trainees in minimal access surgery.

In conclusion, the direction of view of the endoscope had no significant effect on intracorporeal knot tying if the optical axis subtended the same angle with the task surface. A range of 75–150 mm in the distance between the endoscope and the task, and a manipulation angle of 60°, provide the optimum ergonomic conditions for intracorporeal knot tying. Both ability of the surgeon and the effect of practice influence endoscopic task performance.

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Oesophageal motility before and after laparoscopic Nissen fundoplication

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Background Whilst oesophageal manometry outcomes following fundoplication performed by open techniques have been described, detailed reports of changes in manometric parameters following large series of laparoscopic Nissen fundoplication have yet to be described.

Methods An analysis of oesophageal manometry studies performed on patients undergoing laparoscopic Nissen fundoplication at the Royal Adelaide Hospital was performed to quantitate the effect of surgery and to determine whether manometric indicators of adverse surgical outcome could be identified. The original manometric recordings from a subset of 103 patients were reviewed. Only patients who had undergone preoperative and postoperative examinations in this department, and assessment by an independent investigator using a standardized clinical questionnaire, were included in the study.

Results Mean resting lower oesophageal sphincter (LOS) pressure increased from 8·5 to 21·5 mmHg ($P < 0·0001$) following surgery, the mean residual pressure after sphincter relaxation (residual relaxation pressure) increased from 1·2 to 10·8 mmHg ($P < 0·0001$), and oesophageal 'ramp' pressure increased from 10·5 to 20·5 mmHg ($P < 0·0001$). Before operation 88 patients (85 per cent) propagated seven or more of ten wet swallows (normal peristalsis) *versus* 83 (81 per cent) after operation. Of the 15 patients with abnormal peristalsis before surgery, eight regained normal peristalsis after operation, whereas 13 of 88 patients with normal preoperative peristalsis subsequently had defective postoperative peristalsis. Raised postoperative residual relaxation pressure ($r = 0·20$) but not LOS pressure correlated significantly with postoperative dysphagia for liquids. None of the measured manometric parameters correlated with adverse outcomes such as postoperative dysphagia for solids, patient dissatisfaction or gas bloat.

Conclusion Whilst this study documents significant changes in LOS pressure following laparoscopic Nissen fundoplication, a clinically significant correlation between manometric outcome and clinical outcome was not demonstrated.

Recently published American Gastroeneterological Association consensus guidelines do not support routine preoperative manometric assessment before antireflux surgery[1] However, oesophageal manometry is performed in many centres for the routine preoperative investigation of patients undergoing surgery for gastro-oesophageal reflux[2]. As well as documenting lower oesophageal sphincter (LOS) pressure, it is the most useful method of assessment of peristaltic activity and is used by some surgeons to justify modification to standard surgical approaches if patients have motility disorders. Previous studies have demonstrated that Nissen fundoplication results in an increase in the manometrically determined pressures recorded in the LOS zone following surgery[3–6]. Both the resting LOS pressure and the residual pressure following swallow-induced sphincter relaxation (residual relaxation pressure) are increased following Nissen fundoplication[7].

It has been shown recently that when the upper sphincter fails to open normally, a ramp in hypopharyngeal pressure can be measured in the hypopharynx immediately preceding the pharyngeal peristaltic pressure wave[8]. A similar pressure ramp has been demonstrated in the distal oesophagus in an experimental model of oesophageal obstruction at the gastro-oesophageal junction[9]. This pressure correlates with resistance to the passage of a swallowed bolus across the sphincter, but its clinical significance has not been determined and its importance for the assessment of dysphagia after fundoplication is unknown.

Manometric changes following fundoplication performed by open techniques[3–7] have been well documented, although findings have not been uniform. Whilst two recently published small series have reported changes in oesophageal motility before and after laparoscopic fundoplication[10,11], no detailed report of changes in motility in a large series of laparoscopic Nissen fundoplication has been published. This study was performed to measure the effect of laparoscopic Nissen fundoplication on oesophageal motility, including 'ramp' pressure, and to correlate this with independently measured symptom scores in order to determine whether or not changes in oesophageal motility predict adverse clinical outcome.

Patients and methods

Patient selection

Between October 1992 and December 1995, 350 patients underwent a laparoscopic antireflux procedure in this department.

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Patients were included in the study if they had undergone preoperative oesophageal manometry, laparoscopic Nissen fundoplication and postoperative manometry in this department. This enabled subsequent independent review of the original manometry recordings, and the determination of ramp pressures. Patients were excluded if they underwent preoperative manometry examination elsewhere, underwent a laparoscopic partial fundoplication or had not undergone independent clinical assessment more than 3 months following surgery.

Some 103 patients (56 men; age 20–79 (median 54) years) satisfied all of the criteria for inclusion in the study. This group did not differ significantly from the total group in regard to age, sex, weight, operating time and the clinical outcome scores used in the study. Eighty per cent of the overall group had undergone similar postoperative clinical assessment at the time of this study. Manometry was performed between 3 and 6 months after operation (mean 5·5 (95 per cent confidence interval 4·7–6·4).

Operative technique

Laparoscopic Nissen fundoplication was performed using a technique described previously[10]. This technique entailed initial full oesophageal mobilization and posterior hiatal repair. Short gastric vessels were sometimes divided between metal clips. The anterior wall or apex of the gastric fundus was pulled behind the oesophagus to enable construction of a loose 360° fundoplication which was calibrated with a 52-Fr bougie within the oesophageal lumen. Usually three and occasionally four interrupted sutures were used to secure a wrap of approximately 2 cm in length.

Oesophageal manometry

Patients were fasted for 6 h before each study and all medication affecting oesophageal motility was discontinued 2 days earlier if necessary, except proton pump inhibitors which were stopped 5 days before motility studies. Oesophageal manometry was performed using an eight-lumen water-perfused catheter incorporating a sleeve sensor (Dentsleeve, Adelaide, Australia), with signals recorded on a polygraph chart recorder (Model 7D; Grass Instrument Company, Massachusetts, USA). The LOS (or postfundoplication high-pressure zone) was located by the station pull-through technique and the centre of the sleeve was positioned over the LOS. Each lumen of the catheter was connected in series with a pressure transducer (Stratham P231D; Gould, Oxnard, California, USA) and was constantly perfused with degassed distilled water at 0·6 ml/min by a low-compliance pneumohydraulic pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA).

Basal LOS pressure was measured over a 5-min period using a sleeve sensor, followed by measurement of the amplitude and propagation of primary peristalsis, and residual relaxation pressure of the LOS during ten swallows of 5-ml water boluses, always at more than 30-s intervals.

Data analysis

Basal LOS pressure, referenced to intragastric pressure, was determined from the recordings obtained during the initial 5-min resting period. Residual relaxation LOS or gastro-oesophageal junction pressure was measured by averaging the mean minimum relaxation pressure recorded during each of the ten water swallows.

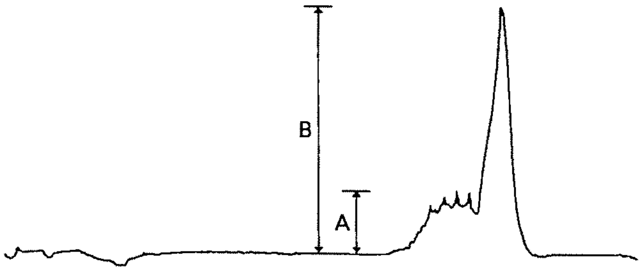

Fig. 1 Distal oesophageal manometric recording in which ramp pressure is readily visualized using a chart speed of 5 mm/s A, amplitude of ramp pressure; B, amplitude of distal oesophageal peristaltic contraction

Lower oesophageal ramp pressure was not measured routinely during the initial manometry study, but was determined subsequently by an independent assessor who reviewed the original manometric recordings. The ramp pressure represented a rise in intraluminal oesophageal pressure occurring just before swallow-induced peristaltic contractions. It was identified immediately proximal to the LOS before operation or proximal to the gastro-oesophageal high-pressure zone after operation. This pressure was determined by measuring the difference between end expiratory basal oesophageal pressure and the maximum pressure of the pressure ramp. Whilst ramp pressure can be identified and measured from conventional manometric recordings which use a polygraph chart recorder paper speed of 100 mm/min, it is more clearly defined when using a faster speed of 5·0 mm/s (*Fig. 1*). Ramp pressure was sought using the faster speed in this study. Individual ramp pressures were measured for each of the ten water swallows used to determine oesophageal peristalsis and residual relaxation pressure, and a mean ramp pressure was calculated for each patient.

Peristalsis was also assessed during each of the water swallows. Propagation was considered to be successful when a peristaltic wave progressed along the entire length of the oesophagus. Successful propagation of seven or more of the ten water swallows was used to define normal oesophageal peristalsis.

Postoperative manometry was performed 3–6 months after operation as part of a follow-up protocol for patients undergoing laparoscopic Nissen fundoplication.

Clinical outcome scores

Clinical outcome following surgery was determined prospectively by applying a standardized questionnaire administered independently by a hospital scientist within 1 month of the postoperative manometric assessment (i.e. 3–6 months after operation). Symptomatic dysphagia was assessed using two visual analogue scales from 0 to 10. These were: severity of dysphagia when swallowing liquids (no dysphagia, 0; total dysphagia, 10) and severity of dysphagia when swallowing solid foods (no dysphagia, 0; total dysphagia, 10). The presence or absence of symptoms suggesting gas bloat was also determined by asking patients whether they ever experienced discomfort due to upper abdominal distension or a sensation of bloating of the upper abdomen, including occasional or mild bloat symptoms. Overall satisfaction with the surgical outcome was also determined using a 0–10 visual analogue scale (completely satisfied, 10; totally unsatisfied, 0).

Statistical analysis

Changes in manometric outcomes before and after fundoplication, and comparisons of different patient groups were assessed using the Mann–Whitney *U* test. Spearman's correlation coefficient was used to determine correlations between clinical and postoperative manometry outcomes.

Results

The effects of laparoscopic Nissen fundoplication on oesophageal body and lower oesophageal sphincter function are summarized in *Table 1*. After operation there were significant rises in resting LOS pressure, residual relaxation pressure and ramp pressure. Fundoplication had variable effects on peristaltic success. Fifteen patients propagated fewer than seven of ten wet swallows before operation. Of these, eight propagated seven or more of ten wet swallows at postoperative manometry. On the other hand, the peristalsis of 13 other patients changed

Table 1 Changes in oesophageal motility following laparoscopic Nissen fundoplication

	Before operation	After operation	P*
Primary peristalsis (%)	90 (85–94)	89 (84–93)	0·38
LOS resting pressure (mmHg)	8·5 (6·8–10·9)	21·5 (19·5–23·5)	<0·0001
Residual relaxation pressure (mmHg)	1·2 (0·78–1·6)	10·8 (9·5–12·0)	<0·0001
Ramp pressure (mmHg)	10·5 (9·9–11·0)	20·5 (19·3–21·6)	<0·0001

Values are mean (95 per cent confidence interval). LOS, lower oesophageal sphincter. *Mann–Whitney *U* test

Table 3 Postoperative oesophageal manometry and symptoms of gas bloat

	Symptoms present ($n = 64$)	Symptoms absent ($n = 39$)	P*
LOS resting pressure (mmHg)	22·2 (19·6–24·7)	20·4 (17·2–23·7)	0·32
LOS nadir pressure (mmHg)	11·4 (9·7–13·0)	9·7 (7·9–11·5)	0·31
Ramp pressure (mmHg)	20·4 (18·9–22·0)	20·5 (19·0–22·0)	0·69

Values are mean (95 per cent confidence interval). LOS, lower oesophageal sphincter. *Mann–Whitney *U* test

Table 2 Relationship between oesophageal manometric findings and dysphagia

	Dysphagia		
	None or mild	Moderate or severe	P*
Dysphagia for solids			
No. of patients	88	15	
LOS resting pressure (mmHg)	21·1 (18·8–23·2)	24·0 (19·9–28·2)	0·14
Residual relaxation pressure (mmHg)	10·6 (9·2–12·0)	11·6 (8·4–14·9)	0·49
Ramp pressure (mmHg)	20·4 (19·2–21·6)	21·1 (16·9–25·4)	0·98
Dysphagia for liquids			
No. of patients	82	21	
LOS resting pressure (mmHg)	20·8 (18·5–23·1)	24·3 (19·8–28·7)	0·12
Residual relaxation pressure (mmHg)	10·1 (8·8–11·5)	13·2 (10·2–16·1)	0·044
Ramp pressure (mmHg)	20·6 (19·3–21·9)	19·8 (16·8–22·8)	0·65

Values are mean (95 per cent confidence interval). LOS, lower oesophageal sphincter. *Mann–Whitney *U* test

from more than seven of ten swallows propagated before operation to fewer than seven after operation.

Correlations between ramp pressure and resting LOS pressure and residual relaxation pressure were assessed before and after fundoplication. A weak but statistically significant correlation was found between preoperative residual relaxation pressure and ramp pressure ($r = 0{\cdot}20$, $P = 0{\cdot}049$). No significant correlation was found between preoperative resting LOS pressure and ramp pressure, and between postoperative ramp pressure and either residual relaxation or resting lower sphincter pressures.

No correlation between clinical outcome and either ramp pressure or peristaltic success was found. A weak but statistically significant correlation was seen between residual relaxation pressure and dysphagia for liquids ($r = 0{\cdot}20$). No significant correlations were evident between residual relaxation pressure and other clinical outcomes, or solid food dysphagia and any clinical outcome.

Dysphagia was related to postoperative manometric findings by defining a large patient group with either mild or no dysphagia (visual analogue score 0–4) and a smaller group with moderate or severe dysphagia (score 4–10) for both solid and liquid substances (*Table 2*). LOS resting pressure was not significantly raised in patients with moderate to severe dysphagia both for liquids and solids. Residual LOS relaxation pressure was greater in patients with more severe dysphagia for liquids ($P = 0{\cdot}044$), but not in patients with dysphagia for solids. Ramp pressure was not increased significantly in patients with more severe dysphagia.

LOS pressure, residual relaxation pressure and ramp pressure were all similar in highly satisfied patients (satisfaction score 7–10) compared with those in less satisfied patients (score 0–6). Manometric outcomes did not correlate with symptoms of gas bloat (*Table 3*).

Discussion

This study documents changes in oesophageal manometry in 103 patients after laparoscopic Nissen fundoplication. Similar increases in resting LOS pressure, residual relaxation pressure and ramp pressure have been reported by other researchers following Nissen fundoplication performed using open surgical techniques[3–6].

Two recently published studies of small groups of patients have described changes in manometric findings after laparoscopic fundoplication. In a study involving 15 patients who underwent laparoscopic Nissen fundoplication, McAnena *et al.*[11] demonstrated an increase in resting LOS pressure from 5 to 11 mmHg, but failed to report either residual relaxation pressures or ramp pressure. In their study, manometry was performed with a triple-lumen perfused catheter, equipped with side hole sensors only rather than a perfused sleeve sensor. A second study reported by Watson *et al.*[12] examined outcomes following a laparoscopic anterior partial fundoplication in 26 patients. Using a solid-state manometry catheter, they found that mean resting LOS pressure increased from 8·4 to 11·5 mmHg. This smaller pressure rise compared with that after Nissen fundoplication perhaps reflects the nature of the partial fundoplication performed.

A ramp in hypopharyngeal pressure has been described recently by Cook *et al.*[8] in patients undergoing upper oesophageal sphincter manometry for Zenker's diverticulum. This ramp is thought to be a measure of sphincter resistance, and as such is believed to correlate with dysphagia. A recent experimental study using a feline model[9] demonstrated that a similar pressure ramp can also be measured proximal to the LOS, and that its magnitude correlates with the degree of obstruction determined by the pressure in a cuff around the LOS. On this basis, the authors believe that the ramp in the distal intraoesophageal pressure during primary peristalsis triggered by swallowing liquids reflects resistance to flow across the LOS. The increase in ramp pressure following fundoplication is consistent with this hypothesis and the known effect of fundoplication on LOS function[6,11]. It might be expected, therefore, that changes in lower oesophageal ramp pressure following Nissen fundoplication would correlate with dysphagia, because of the extrinsic compression caused by the circumferential fundal wrap. However, whilst this study demonstrated a significant rise in the ramp pressure following laparoscopic Nissen fundoplication, it did not correlate with dysphagia, suggesting that other factors such as integrity of primary peristalsis are more important. Measurement of ramp pressure therefore appears to be of no value for the postoperative assessment of patients following antireflux surgery.

Earlier studies in the era of open surgery have suggested that antireflux surgery can result in improvement in postoperative oesophageal peristaltic activity[5]. Whilst the present study did demonstrate improvement in oesophageal primary peristalsis in eight of 15 patients with abnormal preoperative motility, this was counter-balanced by reduced peristalsis in 13 of 88 patients with normal motility initially. Although rates of peristaltic success used to define normal peristalsis vary among different institutions, and range from 70 to 90 per cent, studies using the definition of peristaltic success applied in this study[13,14] suggest that there has been no overall change in oesophageal peristalsis following laparoscopic Nissen fundoplication, and do not support the concept that antireflux surgery improves defective peristalsis. It is acknowledged, however, that it may be necessary to study patients over a much longer follow-up time to be more sure of this statement. It may even be possible that fundoplication could impair peristalsis if it generates sufficient resistance to the passage of a swallowed bolus, especially in patients with low-amplitude peristalsis before operation. The experimental feline study reported by Mittal *et al.*[9] demonstrated impaired peristalsis in cats swallowing larger bolus volumes and in cats with greater distal oesophageal outflow obstruction.

It is widely held that the adverse outcomes of dysphagia and gas bloat syndrome following antireflux surgery are associated with the construction of a tight fundoplication, and that raised LOS pressures measured by postoperative oesophageal manometry will confirm or predict these problems[6,15]. Few studies have examined this belief objectively[6]. The authors have previously found, in a small group of patients, no relationship between resting LOS pressure and dysphagia[16]. On the other hand in a more intensively studied group, in which many patients were studied selectively because of dysphagia, there was a relatively good correlation between resting LOS pressure, residual relaxation pressure, ramp pressure and dysphagia[17].

Of the manometric variables measured in the present study, only postoperative residual LOS relaxation pressure correlated with adverse surgical outcome. Dysphagia for liquids was more likely in patients with higher postoperative residual relaxation pressures. This suggests that it is likely to be a better measure of the degree of obstruction caused by a fundoplication than other manometric parameters measured. Nevertheless, the correlation coefficient of 0·20, whilst statistically significant, does not support a strong clinical correlation.

The lack of a clinically significant correlation between manometric outcome and the clinical outcomes of dysphagia or satisfaction with surgery in this study was unexpected, particularly as other studies have suggested that raised residual relaxation pressure may be associated with dysphagia or other adverse outcomes following fundoplication[6,18]. However, these studies have usually assessed small groups of patients retrospectively. The specific relationship between dysphagia and LOS pressure has not been studied prospectively in a large patient group, using blinded clinical and manometric assessments. Nevertheless, it is possible that the number of patients with severe dysphagia is still too small for the measured increase in lower sphincter resting pressure to reach significance. However, the findings suggest that postoperative oesophageal manometry is of limited value in the assessment of patients undergoing antireflux surgery.

The mechanism of dysphagia following antireflux surgery remains unclear at this stage. It seems likely that other factors, apart from manometrically measured fundoplication tightness, contribute to adverse symptoms following laparoscopic Nissen fundoplication. Whilst resting and residual relaxation LOS pressures may be higher following Nissen fundoplication than partial fundoplication variants[12], the outcomes of randomized trials of Nissen *versus* posterior partial fundoplication have failed to confirm long-term differences in the incidence or severity of dysphagia[19,20]. Randomized trials comparing anterior fundoplication with Nissen fundoplication have yet to be reported. The authors recently demonstrated that preoperative illness behaviour can influence clinical outcomes following laparoscopic fundoplication[21]. This suggests that the aetiology of dysphagia is multifactorial, with further studies needed to understand fully its cause.

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Early adenocarcinoma in Barrett's oesophagus

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Background The results of surgical treatment in 41 patients with early adenocarcinoma of the oesophagus were analysed retrospectively.

Methods The treatment of choice was transhiatal radical subtotal oesophagectomy ($n = 38$); in three patients with adenocarcinoma in the mid or upper thoracic portion of the oesophagus, right transthoracic *en bloc* oesophagectomy was performed.

Results One patient died within 30 days and another within 90 days (4·8 per cent). All tumours were resected completely. Multicentricity of adenocarcinoma in Barrett's oesophagus was detected in six cases and high-grade dysplasia in 28. Some 31 patients had infiltration of the submucosa, whereas in ten, carcinoma was limited to the mucosa. No patient with mucosal adenocarcinoma had lymph node metastases, whereas five of the 31 with submucosal infiltration showed lymph node involvement. The 5-year survival rate of the total group of 41 patients, including postoperative mortality, was 83 per cent. All ten patients with adenocarcinoma limited to the mucosa (pT_{1a}) were alive at 5 years; of 31 with submucosal infiltration (pT_{1b}) 79 per cent survived to 5 years (*P* not significant). Patients without lymph node metastasis had a 5-year survival rate of 81 per cent, compared with 50 per cent for those in the pN_1 category (*P* not significant).

Conclusion Oesophagectomy for early oesophageal adenocarcinoma is safe and leads to a favourable long-term prognosis.

The incidence of Barrett's adenocarcinoma in Europe and North America is increasing. The prognosis of patients with the early stage of this lesion has become important[1–4]. Early oesophageal cancer is defined as a tumour limited to the mucosa or submucosa and consequently offers favourable prerequisites for complete healing after surgical resection[5]. Most previous series of oesophageal pathological tumour stage pT_1 adenocarcinoma included carcinoma of the cardia or were too small for a representative analysis of clinicopathological characteristics and long-term outcome[6–10]. The purpose of this study was to analyse a larger series of patients who had resection of early oesophageal adenocarcinoma to investigate the rate of multicentricity and lymph node involvement, and to evaluate the prognosis according to depth of tumour infiltration and presence of lymphatic metastases.

Patients and methods

Between July 1982 and 30 June 1995, 706 patients had resection for oesophageal cancer (446 squamous cell carcinomas and 260 adenocarcinomas) in the Department of Surgery of the Technical University of Munich. Adenocarcinoma of the oesophagus was defined as a tumour centred more than 1 cm above the anatomical cardia according to preoperative endoscopy and radiography, and postoperative examination of the resected specimen[11,12]. Within this series of adenocarcinomas, 41 patients (16 per cent) had carcinoma limited to the mucosa or submucosa. This excluded patients who were staged as pT_1 after preoperative radiotherapy and/or chemotherapy[5]. Routine preoperative staging included endoscopy, percutaneous ultrasonography, computed tomography and endoscopic ultrasonography (since 1986) Histopathological examination of all resected specimens consisted of a thorough evaluation of tumour stage, residual tumour (R category), grading, and the number of resected and involved lymph nodes[5]. The ratio of the number of infiltrated to resected lymph nodes was termed the lymph node ratio[12]. pT_1 tumours were further subclassified as pT_{1a} (limited to the mucosa) and pT_{1b} (submucosa)[13] Follow-up was performed regularly in the tumour clinic of the Department of Surgery. Data were collected prospectively according to a standard protocol. Follow-up was complete for all 41 patients, including a final examination in February 1996. The median duration of follow-up for the whole series was 5·5 (range 0·7–12·9) years. The median age of the patients was 60 (range 28–82) years. The male:female ratio was 8:1.

The treatment of choice for early adenocarcinoma of the distal oesophagus was transhiatal radical subtotal oesophagectomy and partial gastrectomy[12,14–16]. This included wide incision of the diaphragm from in front of the oesophageal hiatus and exposure of the lower mediastinum by insertion of two long hooks. The perioesophageal tissue of the lower mediastinum between the pericardium and aorta was resected in continuity with the oesophagus. The proximal two-thirds of the lesser curvature of the stomach was removed by linear stapler up to the uppermost point of the fundus. In addition to this partial lymphadenectomy of compartment I, complete lymphadenectomy of compartment II was added[14,17,18]. Three patients with proximal extension of Barrett's change and adenocarcinoma in the mid or upper thoracic portion of the oesophagus had a right transthoracic *en bloc* oesophagectomy with extended mediastinal lymphadenectomy[14]. After both types of resection, the reconstruction was made with a 4–5-cm wide gastric tube fashioned along the greater curvature[12]. The stomach interposition was placed in the posterior mediastinum, and all anastomoses were performed in the neck

Median values and upper quartiles were calculated. Statistical analysis included the Peto–Wilcoxon test; the limit of significance was defined as $P < 0·05$. The survival function was estimated according to Kaplan–Meier, including postoperative mortality[19]. The 5-year survival rate was calculated together with the 95 per cent confidence interval (c.i.)[20]. Statistical analysis was performed with program modules 1L and 2L of the BMDP statistical package, revision 1990 (BMDP, Cork, Ireland).

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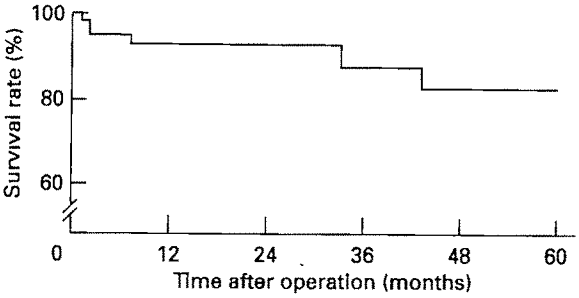
Results

Some 28 of the 41 patients were symptomatic; the main complaints were dysphagia, epigastric pain and retrosternal pressure. However, 13 patients were asymptomatic; their tumours were detected during oesophagogastroscopy for various reasons. Eight of the 13 asymptomatic patients had endoscopy in the course of a regular surveillance programme for Barrett's oesophagus. The adenocarcinomas detected by this programme included six mucosal and two submucosal tumours.

Postoperative surgical and general complications occurred in 18 of the 41 patients; one patient died within 30 days of operation, and another within 90 days (4·8 per cent). In all cases, complete resection (R_0) of the tumour was achieved. On average, 23 (range 10–48) lymph nodes were removed. Some 36 early adenocarcinomas had developed in a columnar cell-lined lower oesophagus, as proven by endoscopy and histology, with a minimum length of 3 cm. The mean length of Barrett's oesophagus in these 36 patients was 6·3 (range 3–15) cm. The mean maximum extent of all pT_1 carcinomas was 2·5 (0·1–8·0) cm.

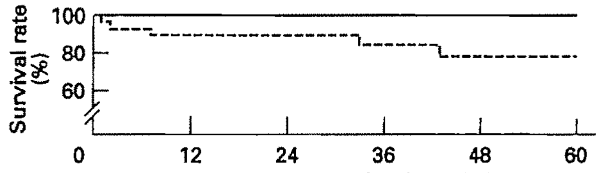
In ten of the 41 patients the carcinoma was limited to the mucosa (pT_{1a}), including three patients with slight encroachment of the muscularis mucosae. Thirty-one patients had infiltration of the submucosa (pT_{1b}). In six cases there was multicentric tumour development in Barrett's oesophagus on histology. Twenty-eight cases showed high-grade dysplasia within the specialized epithelium; 13 had low-grade dysplasia. Histological grading[5] identified five G_1, 26 G_2, nine G_3 and one G_4 tumour. No involved lymph nodes were detected in 36 of the 41 patients (pN_0), whereas five had lymph node involvement (pN_1). No patient with mucosal adenocarcinoma had lymph node metastases; all patients with lymphatic spread had submucosal infiltration (five of 31 cases). The ratio of infiltrated to removed lymph nodes in the five pN_1 cases was: 1:41, 1:10, 2:12, 3:13 and 7:17. On average, 19 per cent of the removed lymph nodes were infiltrated in the pN_1 carcinomas. Regional lymph nodes were involved in four cases (paraoesophageal, paracardial or lesser curvature); however, in one patient a cervical lymph node was also infiltrated ($pT_1\ N_1\ M_{1\,LYM}$).

Two patients had second primary cancers: one had had thyroidectomy for papillary thyroid carcinoma 18 months before oesophagectomy; the other developed squamous cell cancer of the lung 11 years after oesophagectomy. The causes of death after long-term follow-up were postoperative mortality in two and distant metastases in four. Some 83 per cent (95 per cent c.i. 80–85 per cent)) of the total group of 41 patients with oesophageal adenocarcinoma survived for 5 years (*Fig. 1*). There was a limited number of cases in the subgroups, and no significant differences were found between the survival curves of patients with mucosal or submucosal infiltration (5-year survival rate 100 per cent *versus* 79 (95 per cent c.i. 75–82) per cent respectively) and pN_0 or pN_1 category (5-year survival rate 81 (95 per cent c.i. 78–83) per cent *versus* 50 (95 per cent c.i. 25–71) per cent respectively) (*Figs 2* and *3*). All patients with carcinoma detected in the course of endoscopic surveillance have survived disease-free for 1·2, 1·3, 1·7, 4·1, 4·3, 5·9, 8·1 and 12·2 years after oesophagectomy; for patients without diagnosis by surveillance the 5-year survival rate was 79 per cent (*P* not significant).



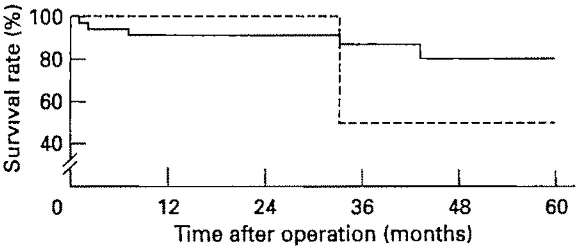
No. at risk	41	31	27	21	15	12

Fig. 1 Survival of 41 patients with resected pT_1 adenocarcinoma of the oesophagus



No. at risk						
pT_{1a}	10	7	7	7	4	2
pT_{1b}	31	24	20	14	11	10

Fig. 2 Survival of 41 patients with resected pT_1 adenocarcinoma of the oesophagus, comparing infiltration of the mucosa (———, pT_{1a}) and submucosa (– – – –, pT_{1b})



No. at risk						
pN_0	36	26	23	19	13	10
pN_1	5	5	4	2	2	2

Fig. 3 Survival of 41 patients with resected pT_1 adenocarcinoma of the oesophagus, comparing pN_0 (———) and pN_1 (– – – –) categories

Discussion

It is desirable to detect oesophageal adenocarcinoma in the T_1 stage because prognosis is significantly correlated to pT category[12]. The most significant variation in long-term survival is found between pT_1 and pT_2 tumours caused by an increase in lymph node metastasis[12,13]. As the columnar cell-lined lower oesophagus is premalignant, endoscopic surveillance programmes have been initiated to detect malignant degeneration of Barrett's epithelium as early as possible. However, the impact of this surveillance on the long-term results of oesophagectomy for carcinoma has been demonstrated in only one study[21] and in several anecdotal reports[7,22–29]. The present analysis supports the development of surveillance programmes for Barrett's oesophagus, as eight early adenocarcinomas (mostly mucosal tumours) were found as a result of regular endoscopic review. These eight patients also had a potentially more favourable outcome than the group diagnosed without surveillance. Early detection of adenocarcinoma is difficult because one-third of patients are asymptomatic, and the others often have uncharacteristic symptoms. Therefore, the frequency of detection of early oesophageal adenocarcinoma used to be low. Centres specializing in oesophageal surgery currently report rates of early cancer in resected oesophageal adenocarcinoma of 10·7[22], 21·5[23] and 36·3[29] per cent, similar to the rate of 16 per cent in the present series. These rather high rates may be due to an increasing awareness of the malignant potential of Barrett's oesophagus. They may also represent first results of surveillance programmes in specialized centres.

An important finding in this study is the frequency of multicentricity of early Barrett's carcinoma and the rate of concomitant high-grade dysplasia in Barrett's epithelium. The multifocal development of this lesion with additional foci of high-grade dysplasia or carcinoma *in situ* has been described by others[7,24,25,30]. It is generally accepted that the whole columnar cell-lined lower oesophagus must be resected together with the adenocarcinoma. The multifocal nature of this carcinoma is an argument against local endoscopic mucosectomy for early lesions.

Another important result of histological examination is the rate and localization of lymph node metastases. Lymphatic involvement should not be expected in mucosal adenocarcinoma. However, preoperative distinction between mucosal and submucosal infiltration by endoscopy or endoscopic ultrasonography is difficult. Therefore, the treatment of choice for early oesophageal adenocarcinoma is radical subtotal oesophagectomy and lymphadenectomy. This can be performed by means of a transhiatal approach because lymphatic metastases of adenocarcinoma usually involve the lower thoracic, paraoesophageal and paracardial nodes[12,31]. As most patients with pN_1 lesions in this series had involvement only of regional lymph nodes and had an infiltration rate of less than 30 per cent of removed nodes, lymphadenectomy should be worthwhile for early adenocarcinoma and may improve the prognosis[12]. The long-term results for pT_{1a} carcinoma suggest that oesophageal adenocarcinoma limited to the mucosa may be cured by surgical resection, a finding confirmed by five other smaller series[22,23,29,32,33]. Although the difference in survival between patients with mucosal or submucosal infiltration was not significant in the present study owing to the small numbers in these subgroups, the overall trend seems to be obvious. The non-significant difference between the survival curves of patients with pN_0 or pN_1 lesions could be interpreted similarly. Early detection of oesophageal adenocarcinoma is worthwhile because the risks of oesophagectomy are low and the long-term prognosis is good.

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Population-based study of diagnosis, treatment and prognosis of gastric cancer

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Background Gastric cancer remains a common cancer with a poor prognosis. Improving trends seen in Japan have not yet been observed in Western countries.

Methods A population-based series of 1329 patients with gastric cancer diagnosed over an 18-year period in Côte d'Or, France, was used to establish time trends in diagnostic strategy, treatment and prognosis.

Results The use of endoscopy alone increased from 2·7 per cent in 1976–1978 to 76·6 per cent in 1991–1993 ($P<0\cdot0001$). This trend was associated at first with a significant decrease in the use of radiography alone, then by a significant decrease in the use of both radiography and endoscopy. The proportion of resections for cure increased from 37·9 per cent in 1976–1978 to 50·0 per cent in 1991–1993 (mean 3-year variation +5·8 per cent, $P<0\cdot01$). The proportion of cases confined to the gastric wall increased from 6·1 to 11·7 per cent (mean 3-year variation +13·1 per cent, $P<0\cdot01$), while the proportion of other stages remained stable. The operative mortality rate decreased dramatically from 25·6 per cent in 1976–1978 to 13·6 per cent in 1991–1993 ($P<0\cdot001$) and the 5-year relative survival rate rose from 12·8 per cent in 1976–1978 to 26·4 per cent in 1988–1990 ($P<0\cdot001$).

Conclusion This study has demonstrated that improvements in the care of patients with gastric cancer have been achieved, but that further progress may be made.

Although there has been a continuous decrease in its overall incidence throughout the world during the past decades[1,2], gastric cancer remains a common and serious disease[3]. In France, it ranks fifth after colorectal, breast, lung and prostate cancers[4] with an estimated 8700 new cases each year. The optimistic features reported in Japanese series, such as an increase in early diagnosis and an improved 5-year survival rate, have not been observed elsewhere in the world. In Western countries the prognosis of patients with gastric cancer remains poor because diagnosis is still late, stage at diagnosis is advanced and the operative mortality rate is unacceptably high in the opinion of many practitioners, although surgical resection offers the only prospect of cure. Developments in diagnostic investigations seem to have spread progressively, as has more radical surgery, as initiated in Japan, particularly in specialized centres. However, the impact of these changes at the population level is not known. Population-based studies, recording all cases diagnosed in a well-defined population, represent the only way to assess improvements in the management of gastric cancer.

The aim of this study was to draw a picture of time trends in diagnostic strategy, treatment and prognosis of gastric carcinoma diagnosed during the period 1976–1993 in a non-selected community-based series of patients.

Patients and methods

A population-based cancer registry records all digestive tract cancers in the resident population of Côte d'Or in Burgundy, France. The population was 494000 according to the 1990 census figures from the Institut National de la Statistique et des Etudes Economiques. Information is obtained routinely from pathologists, medical specialists (mostly gastroenterologists, surgeons and oncologists), general practitioners and death certificates to ensure completeness of data. One university hospital, one cancer hospital, four local hospitals and five private hospitals provide treatment for patients with gastric cancer in the Côte d'Or region. The quality and completeness of the registry is certified every 4 years by an audit of the National Institute for Health and Medical Research.

A total of 1329 patients with gastric cancer, recorded between 1976 and 1993, were considered for the study. The mean annual age-standardized incidence was 15·0 per 100000 in men and 9·4 per 100000 in women. Mean variation in incidence, by 3-year period, was −6·4 per cent (95 per cent confidence interval (c.i.) −14·5 to 1·7 per cent; $t=-2\cdot18$, 4 d.f., $P=0\cdot10$) in men and −9·1 per cent (c.i. −18·7 to 0·6 per cent; $t=-2\cdot61$, 4 d.f., $P=0\cdot06$) in women.

Patients were categorized into three age groups: under 65 years, 65–74 years, and 75 years and over. Place of residence was coded as Dijon city, other urban areas (towns of more than 2000 inhabitants) and rural areas. Tumour site was classified according to the International Classification of Diseases for Oncology[5]. Treatment procedures were divided into resection for cure (macroscopic resection of all tumoral tissue and no microscopic evidence of surgical margin involvement), palliative resection, bypass, exploratory laparotomy and medical treatment. Operative mortality was defined as death within 30 days after surgery. Stage at the time of diagnosis was based on hospital records and pathology records. Six stages were defined according to the tumour node metastasis (TNM) classification[6]: tumour limited to the gastric wall ($T_{1-2}N_0M_0$), involvement of serosa ($T_{3-4}N_0M_0$), lymph node metastasis (N^+M_0), locoregional extension (patients operated on, without visceral metastasis but with irresectable cancer), visceral metastasis (M^+) and unclassified (patients not operated on, without detected metastasis). Survival of patients was ascertained from death certificates, registrar of the place of birth and place of residence, or from practitioners. The life status was known for 1316 patients (99 per cent) in December 1995.

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Statistical analysis

Time trends were established by 3-year periods by means of linear regression. Mean variations of proportions, together with the 95 per cent c.i. were calculated using the coefficient and the residuals of the regression equation. Non-conditional logistic regression was used to identify risk factors independently and significantly associated with the final treatment (surgery for cure or other treatment) and with the risk of operative death.

Analysis was carried out with the BMDP (Los Angeles, California, USA) software package. Relative survival rates were computed using the Relsurv 1·0 program for relative survival (Hedelin, Strasbourg, France). They were defined as the ratio of the observed to the expected survival rate. Relative survival curves were predicted curves. Multivariate analysis was performed using a relative survival model with proportional hazard applied to the net survival by interval[7]. This model makes it possible to calculate relative risks. The variables tested in the model were age, sex and all the studied variables significant at the 5 per cent level in the univariate analysis. The multivariate model was fitted with a backward procedure. The significance of covariates was tested by the likelihood ratio test

Results

Time trends in diagnostic strategy

Diagnostic strategy changed over time (*Table 1*). The use of radiography alone decreased progressively: −39·1 per cent per 3-year period (c.i. −46·1 to −32·1 per cent; $t = -15{\cdot}54$, 4 d.f., $P < 0{\cdot}001$), whereas the use of endoscopy alone increased: +87·9 per cent per 3-year period (c.i. 56·4 to 119·4 per cent; $t = 7{\cdot}75$, 4 d.f., $P < 0{\cdot}001$). The proportion of patients having both examinations was stable during the first three periods, then decreased dramatically during the following periods.

The proportion of histologically verified cases increased from 81·1 per cent during 1976–1978 to 98·9 per cent during 1991–1993. The mean 3-year period variation was +3·7 per cent (c.i. 1·5–5·9 per cent; $t = 4{\cdot}63$, 4 d.f., $P < 0{\cdot}01$). This increase was more pronounced for patients older than 74 years, +7·1 per cent per 3-year period (c.i. 2·1–12·2 per cent; $t = 3{\cdot}9$, 4 d.f., $P < 0{\cdot}02$), than in younger patients, +1·7 per cent per 3-year period (c.i. 0·9–2·4 per cent; $t = 6{\cdot}1$, 4 d.f., $P < 0{\cdot}01$). The differences related to age disappeared progressively. In the first study period (1976–1978) the proportion of histologically verified cases was 91·5 per cent in those aged under 75 years and 66·7 per cent in those over this age. It was respectively 100 and 97·9 per cent in the last study period (1991–1993).

Time trends in treatment and stage at diagnosis

Time trends in treatment are given in *Table 2*. The proportion of resections for cure increased progressively from 37·9 per cent in 1976–1978 to 50·0 per cent in 1991–1993. The mean 3-year period variation was +5·8 per cent (c.i. 3·1–8·5 per cent; $t = 5{\cdot}9$, 4 d.f., $P < 0{\cdot}01$). This increase was associated with a decrease in the proportion of patients treated surgically but without resection, −10·5 per cent per 3-year period (c.i. −15·8 to −5·2 per cent; $t = -5{\cdot}52$, 4 d.f., $P < 0{\cdot}02$), and of patients not operated on, −4·8 per cent per 3-year period (c.i. −9·5 to −0·02 per cent; $t = -2{\cdot}78$, 4 d.f., $P = 0{\cdot}05$). There was no significant variation in the proportion of palliative resections. The effect of the period of diagnosis, sex, age group and place of residence on the rate of resection for cure was evaluated in a multivariate logistic regression. None of these factors was associated significantly with final treatment for cure. These data confirm that there was no significant increase in the proportion of cases resected for cure over time, independently of other studied factors.

There was no significant overall variation in stage at diagnosis during the different periods studied. The most important variation was an increase of tumours not extending beyond the gastric wall. The proportion in this group rose from 6·1 to 11·7 per cent, a variation of 13·1 per cent per 3-year period (c.i. 7·6–18·6 per cent; $t = 6{\cdot}6$, 4 d.f., $P < 0{\cdot}01$).

Table 1 Time trends in diagnostic strategy

Period	No. of patients	Radiography alone	Endoscopy alone	Radiography and endoscopy	Other
1976–1978	264	62 (23·5)	7 (2·7)	184 (69·7)	11 (4·2)
1979–1981	193	27 (14·0)	29 (15·0)	131 (67·9)	6 (3·1)
1982–1984	248	19 (7·7)	47 (19·0)	176 (71·0)	6 (2·4)
1985–1987	227	10 (4·4)	86 (37·9)	122 (53·7)	9 (4·0)
1988–1990	209	6 (2·9)	148 (70·8)	45 (21·5)	10 (4·8)
1991–1993	188	4 (2·1)	144 (76·6)	36 (19·1)	4 (2·1)

Values in parentheses are percentages. $P < 0{\cdot}0001$ (χ^2 test)

Table 2 Time trends in treatment

Period	No. of patients	Resection for cure	Palliative resection	Laparotomy, bypass, other	No operation
1976–1978	264	100 (37·9)	19 (7·2)	41 (15·5)	104 (39·4)
1979–1981	193	82 (42·5)	24 (12·4)	26 (13·5)	61 (31·6)
1982–1984	248	103 (41·5)	24 (9·7)	35 (14·1)	86 (34·7)
1985–1987	227	109 (48·0)	21 (9·3)	28 (12·3)	69 (30·4)
1988–1990	209	103 (49·3)	22 (10·5)	22 (10·5)	62 (29·7)
1991–1993	188	94 (50·0)	22 (11·7)	16 (8·5)	56 (29·8)

Values in parentheses are percentages. $P = 0{\cdot}13$ (χ^2 test)

Table 3 Factors associated with operative death

	Odds ratio*	*P*†
Age at diagnosis (years)		<0·0001
<65	1	
65–74	1·90 (1·13–3·20)	
≥75	4·02 (2·41–6·70)	
Sex		0·22
M	1	
F	1·28 (0·86–1·90)	
Period of diagnosis		<0·0001
1976–1978	1	
1979–1981	1·03 (0·59–1·84)	
1982–1984	0·66 (0·38–1·15)	
1985–1987	0·36 (0·19–0·68)	
1988–1990	0·27 (0·14–0·55)	
1991–1993	0·41 (0·21–0·80)	
Location of tumour		<0·001
Lower third (antrum)	1	
Middle third (body)	1·44 (0·83–2·50)	
Cardia and upper third	2·25 (1·38–3·68)	
More than one site	3·07 (1·80–5·24)	
Final treatment		<0·001
Resection for cure	1	
Palliative resection	1·45 (0·87–2·43)	
Other surgical procedure	2·42 (1·57–3·74)	

Values in parentheses are 95 per cent confidence intervals. *Logistic regression carried out among patients treated with a surgical procedure, including exploratory laparotomy. †χ^2 test

Table 4 Multivariate analysis of relative survival for gastric cancer

	Relative risk	*P**
Age group (years)		<0·0001
<65	1	
65–74	1·22 (1·02–1·46)	
>74	1·52 (1·28–1·80)	
Period of diagnosis		<0·0001
1976–1978	1	
1979–1981	0·93 (0·75–1·15)	
1982–1984	0·91 (0·74–1·10)	
1985–1987	0·69 (0·56–0·85)	
1988–1990	0·68 (0·54–0·85)	
1991–1993	0·77 (0·62–0·97)	
Location of tumour		<0·002
Middle third (body)	1	
Lower third (antrum)	1·14 (0·93–1·39)	
Cardia and upper third	1·31 (1·08–1·60)	
More than one site	1·30 (1·05–1·61)	
Stage at diagnosis		<0·00001
Limited to the gastric wall	1	
Serosa invaded	4·22 (2·25–7·90)	
Lymph node metastasis	7·19 (3·91–13·20)	
Locoregional extension without resection	14·52 (7·79–27·08)	
Visceral metastasis	23·04 (12·56–42·30)	
Unclassified	12·67 (6·87–23·38)	

Values in parentheses are 95 per cent confidence intervals. *Likelihood ratio test

Time trends in operative mortality

The operative mortality rate decreased from 25·6 per cent for 1976–1978 to 13·6 per cent for 1991–1993 ($P<0·001$). The corresponding values were 16·0 and 11·7 per cent after surgery for cure, 26·3 and 13·6 per cent after palliative resection and 48·8 and 25·0 per cent after bypass and exploratory laparotomy. The overall mean 3-year period variation was −17·3 per cent (c.i. −33·5 to −1·2 per cent; $t=-2·97$, 4 d.f., $P<0·05$).

Age at diagnosis, sex, period of diagnosis, cancer site and final treatment significantly influenced operative mortality in the univariate analysis. The effect of these variables was evaluated in a multivariate logistic regression (*Table 3*). Age, period of diagnosis, cancer site and final treatment were independently associated with the risk of operative death. Patients aged 75 years and over were more than four times more likely to die during the postoperative period than those aged under 65 years. The risk of operative death decreased over the first four periods studied, then became stable. There was a threefold decrease in the operative mortality rate between 1976–1978 and the last three study periods ($P<0·0001$). Non-resected patients had a significantly higher risk of operative death than those who had resection.

Time trends in survival

Relative survival curves for the first five periods are given in *Fig. 1*. The last period is too recent to provide long-term survival rates. Very similar survival rates were observed for the first three periods. Prognosis improved in 1985–1987 and was even better in 1988–1990. The 5-year relative survival rate rose from 12·8 per cent in 1976–1978 to 26·4 per cent in 1988–1990 ($P<0·001$). Stage at diagnosis was an important determinant of prognosis, which also depended on age and cancer site, whereas sex and place of residence were not significant prognostic factors. Significant variables in the univariate analysis were analysed with Esteve's relative survival model (*Table 4*). Stage at diagnosis was a major prognostic factor independently of other studied factors. Risk of death for patients with lymph node metastasis was more than seven times greater than that for those with lesions limited to the gastric wall. Period of diagnosis and age were also independent significant factors. As demonstrated in the univariate analysis, risk of death decreased significantly after the 1982–1984 period.

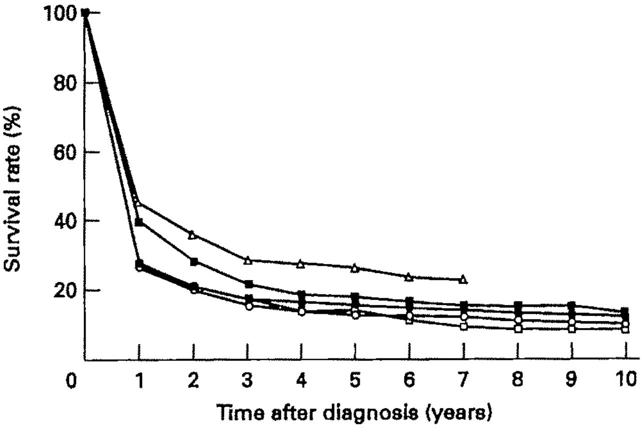

Fig. 1 Overall relative survival curves for the first five periods of diagnosis: ○, 1976–1978 ($n=264$); ●, 1979–1981 ($n=192$); □, 1982–1984 ($n=248$); ■, 1985–1987 ($n=222$); △, 1988–1990 ($n=205$)

Discussion

The data reported here have the advantage of including all cases of gastric cancer diagnosed in a well defined

French population over an 18-year period, including those not treated and those not verified histologically. Information on diagnostic criteria and treatment were available for all patients and survival data were also exhaustive with complete follow-up in 99 per cent of cases. This study was thus carried out without the referral bias that often occurs in hospital-based series. In these series, which often emanate from surgical centres, data on therapeutic approach and prognosis are more favourable than those reported in community-based series. This is well illustrated by comparison of hospital-based[8–10] and population-based[11–13] reports in France as well as in the UK[3,14] and Sweden[15].

No data are available in the literature concerning trends in diagnostic strategy of patients with gastric cancer at a population level. The present data demonstrate significant changes in diagnostic strategy. The use of endoscopy has increased, progressively becoming the only diagnostic examination. As the rate of laparotomy has not increased over time, this trend in diagnostic strategy is probably the explanation for the increase in histologically verified cases.

These dramatic changes in diagnostic strategy were associated with less impressive trends in treatment and stage at diagnosis. The proportion of cases resected for cure increased from 37·9 per cent during the first study period to 50·0 per cent during the last period. As far as stage at diagnosis is concerned, the present authors used the classification proposed by Fielding *et al.*[16] which takes into account the TNM classification[6] and final treatment. There was an insignificant variation in stage at diagnosis. In the literature, reports concerning time trends in treatment at a population level remain scarce[3,11,12]. Trends similar to those observed in the Côte d'Or area have been reported. Previous studies have already stressed that the development of endoscopy was associated with relatively minor progress in gastric cancer care[17]. This can be explained by the fact that, when symptoms occur, the tumour has already spread.

One of the most obvious trends in the management of patients with gastric cancer is the reduction in operative mortality rate. This reduction was observed after surgery for cure, as well as after palliative resection, bypass and exploratory laparotomy; this trend may be attributable to improved surgical techniques, but probably mainly to improved anaesthetic techniques, perioperative nutritional support and general care. It must be stressed that this has been achieved even though the proportion of patients referred for potentially curative resection has increased. A decrease in operative mortality rate was not observed in an analysis of the Birmingham Regional Cancer Registry data in the UK[3], or in the French registry from Calvados[11]; however, in the French study[11] the 10-year study period from 1978 to 1987 was probably too short to observe significant trends. Age at diagnosis was the other main factor influencing the operative mortality rate. Although important progress has been achieved, as reported in a hospital-based series review[18], the operative mortality rate remains relatively high. In 1991–1993 it varied between 11·7 and 25·0 per cent according to the final treatment. Further progress can still be expected over the next decade.

The prognosis of patients with gastric cancer remains poor in population-based statistics. In the Eurocare study[19], covering the period from 1978 to 1987 and including ten Western European countries, the 5-year relative survival rate varied between 19 per cent in Switzerland and 6 per cent in England and Wales. In this study survival rates did not improve over time. The study period was probably too short to observe significant variations. The present data, as well as Norwegian[20] and Finnish[21] findings (covering the period from 1953 to 1975) and Slovenian data[22] (1963–1990), demonstrated a slight but significant improvement in prognosis over time. In contrast, there was no significant change in prognosis in the Netherlands between 1955 and 1994[23]. The decrease in operative mortality rate is one of the major components of an overall decrease in mortality rate. Most of the benefit in survival was already obtained after 1 year. The slight increase in the proportion of cases resected for cure and of tumours limited to the gastric wall has probably also played a role. The improvement in survival remained significant after adjustment for other prognostic factors such as age, stage at diagnosis and location of tumour. It is widely accepted that stage at diagnosis is the main prognostic factor. This indicates that a significant improvement in prognosis will be achieved by means of earlier diagnosis.

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British Journal of Surgery 1997, 84, 1479–1484

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Perianal sepsis in children

Sir

In *Table 2* of this article by Messrs Nix and Stringer (*Br J Surg* 1997; 84: 819–21) the list of rare aetiological factors in perianal sepsis in children did not include threadworms. We have recently treated two children with threadworm infections confirmed on proctoscopy during surgical treatment of anorectal sepsis We presumed that the pathophysiology of the sepsis was related to inflammation of the anal glands caused by the presence of the threadworms in the anal canal with secondary bacterial infection.

Proctoscopy is an essential part of the management of anorectal sepsis in children and looking for threadworms as an underlying cause should be included.

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Endothelin 1 is a mediator of intimal hyperplasia in organ culture of human saphenous vein

Sir

I read with interest the paper by Masood *et al.* (*Br J Surg* 1997; 84: 499–503) describing endothelin (ET) 1 stimulation of vascular smooth muscle cell (VSMC) replication and neointima formation in an organ culture of human saphenous vein. Some of our recent observations on the regional distribution of immunoreactive ET-1 receptor subtypes (ET$_A$ and ET$_B$) in porcine saphenous vein/carotid artery interposition grafts may be of interest. In this model substantial neointima formation and medial thickening occurs 1 month after surgery[1] with abundant immunoreactive ET-1 in the endothelium, neointima and media of vein grafts[2] and dense ET-1 receptor binding (predominantly ET$_A$) in the media and neointima of the vein graft[2] Moreover, the relative overall density of ET$_A$ receptors in the different vessels varied. In ungrafted saphenous vein density was greater than in vein graft and, in turn, density in the vein graft was greater than that in carotid artery[2]. The initially high level of ET$_A$ receptors in ungrafted saphenous veins may render this conduit susceptible to neointima formation, since ET-1 is a mitogen for VSMCs according to the present study by Masood *et al.* and Ohlstein and Douglas[3]. Saphenous vein grafts are distended routinely as part of surgical preparation and are subjected to arterial pressure and high shear stress after implantation, all of which elicit ET-1 release from VSMCs and endothelial cells[4] Increased ET-1 content and ET$_A$ receptors are associated with atherogenesis[3] which, when superimposed on neointima formation, contributes to vein graft failure[1,4].

In contrast, a predominance of the ET$_B$ receptor subtype is associated with microvessels in the adventitia of vein grafts[2] and immediately after implantation of the saphenous vein the absence of functioning vasa vasorum may compromise oxygenation resulting in hypoxia-elicited VSMC replication and neointima formation[4]. Rapid microangiogenesis may constitute an important adaptation to increased thickness and altered oxygen requirements of vein grafts[4]. Indeed, ET-1 (through activation of ET$_B$ receptor subtypes) promotes microangiogenesis through the induction of migration of endothelial cells, a progenitor of microvessel formation[5].

These findings may be of relevance to the pharmacological treatment of vein graft disease when administration of ET$_A$ antagonists may differentially inhibit neointima formation without influencing ET$_B$ receptor-linked microvessel formation. In contrast, administration of ET$_B$ receptor antagonists would have no effect on neointima formation and might exacerbate graft pathology through negative effects on microangiogenesis. These possibilities warrant further investigation

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Major vascular injury during laparoscopy

Sir

Major vascular injury during routine laparoscopic surgery may require a large incision for access and postoperative care in the intensive treatment unit. Patient thoughts regarding blame and litigation may follow, especially if the original operation, often a minor one, is not completed. We wish to add one further recommendation to those offered by Witz and Lehmann (*Br J Surg* 1997; 84: 800) that vascular surgeons called to manage such a vascular emergency help reduce subsequent dissatisfaction by completing the proposed procedure, if it is safe to do so. Carrying out sterilization, for example, adds nothing to subsequent morbidity, removes the need for subsequent reoperation for the planned procedure, and is a good example of risk management.

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Laparoscopic surgery is associated with less tumour growth stimulation than conventional surgery: an experimental study

Sir

We read the paper by Dr Bouvy (*Br J Surg* 1997; 84: 358–61) with interest and have comments on the statistical analysis and experimental design of the study. They indicated that the normal distribution is verified by a histogram but in *Table 1* one can observe that the standard deviation of each group is large, resulting in coefficients of variation greater than 50 per cent This value should not exceed 30 per cent in normally distributed data. A normal distribution concerning the whole group of animals is not sufficient to perform parametric tests such as analysis of variance (ANOVA), Student's *t* test, etc Each group should be normally distributed within itself and with group sizes of less than 15 this is a questionable claim. The correct statistical approach would have been to have used the non-parametric Kruskal–Wallis test instead of ANOVA[1].

Bacteria, endotoxin and particulate material can be absorbed by the diaphragmatic lacunae and reach the systemic circulation via the thoracic duct[2]. The importance of parathymic lymph nodes that drain the peritoneal cavity on local eradication of tumour cells was stressed in an earlier well conducted study[3] For these reasons it might be more relevant to take into account tumour growth in the parathymic lymph nodes and free tumour cells in the peripheral blood.

In the second part of the study the authors inoculated tumour cells into the renal subcapsular space via laparotomy. Laparotomy is one of the major variables of the study and one group of animals underwent two laparotomies, while the laparoscopy group had only one. The effect of opening the peritoneum has been shown to be detrimental on immunity by others[4,5]. The effect of an additional laparotomy on immunity is not well documented but may cause a linear or exponential effect If exponential, immunity may be more depressed than expected in the laparotomy group. It might have been more appropriate to use a dorsal flank incision for inserting the tumour into the renal subcapsular area in both groups to eliminate the effect of additional laparotomy

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Herniography for groin pain of uncertain origin

Sir

Mr MacArthur and colleagues reviewed their experience of herniography for the diagnosis of groin hernia (*Br J Surg* 1997; 84: 648–5). In agreement with previous published studies, they conclude that the technique is useful in patients where there is diagnostic uncertainty before surgical exploration. As with previous reports, however, there is a group of patients who remain symptomatic without a definitive diagnosis. In their series five of 34 patients remained symptomatic. We have recently reported[1] a series of 63 consecutive patients who underwent herniography over a 3-year period in which 26 hernias in 23 patients were detected Of the 40 patients with a negative herniogram, four patients underwent surgical exploration because of the persistence of symptoms and the lack of a definitive diagnosis. Three of these patients were found to have definite inguinal hernia and all gained symptomatic relief from repair. In our experience, therefore, the technique has a false-negative rate of at least 7·9 per cent. We would therefore agree with MacArthur *et al.* that herniography is useful in the diagnosis of hernia in the absence of other clinical evidence, but also suggest that the negative herniogram in the absence of clinical improvement and a definitive diagnosis should not preclude the patient from surgical exploration.

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Experimental study in bile duct-ligated rats of vasopressin and preoperative volume loading to prevent hypotensive crises

Sir

We read with interest the paper by Jacob *et al.* (*Br J Surg* 1997; 84: 483–7) describing maintained pressor responsiveness to vasopressin in rats with bile duct ligation of 3 days' duration and reversed susceptibility of jaundiced rats to haemorrhagic hypotension with prophylactic volume loading.

Obstructive jaundice is known to cause reduced peripheral resistance, resulting in vasodilatation which is refractory to vasoactive amines[1]. Experimental and clinical studies in obstructive jaundice have demonstrated impaired myocardial function with reduced left ventricular performance and blunted contractile response to inotropic stimulation[2–4]. It appears, therefore, that in obstructive jaundice the contractility of the entire cardiovascular tree is suppressed and therefore a suitable pharmacological agent to treat hypotensive crises would be desirable. The study by Jacob *et al.* has demonstrated the usefulness of vasopressin in jaundiced rats to induce a normal pressor response.

The second objective was to evaluate the influence of volume loading in preventing hypovolaemia and the increased susceptibility to hypotension Direct evidence of marginal hypovolaemia in obstructive jaundice has recently been demonstrated, both in an experimental model and in humans, from body water compartment analyses using tracer isotopes[5,6]. We agree with the authors' conclusion that preoperative volume loading in obstructive jaundice is advantageous. It corrects any pre-existing latent hypovolaemia, reverses the sensitivity to haemorrhage, improves the function of the cardiovascular system, and ultimately ensures the maintenance of adequate renal perfusion. In our own clinical experience, careful attention to perioperative fluid and electrolyte balance in addition to prophylactic volume expansion before therapeutic intervention reduces the incidence of postoperative renal dysfunction[7].

Of the four fluids evaluated, mannitol appeared to be the most effective in reversing the increased susceptibility to haemorrhage in cholestasis and it was suggested that, in addition to providing volume expansion, it acts as an antioxidant It may increase renal blood flow and increase the tubular production of urine by its diuretic action but the only prospective trial to assess its effect in jaundiced patients failed to demonstrate any significant benefit and showed that postoperative deterioration in renal function was actually greater in patients receiving mannitol[8]. The routine use of mannitol in this setting is not effective and may even be detrimental if it exacerbates pre-existing hypovolaemia and hypotension due to its osmotic potential.

Clearly, further studies on the systemic and renal haemodynamics of obstructive jaundice are required. At present, we suggest caution in the routine perioperative use of mannitol in jaundiced patients as it may initially improve urine output but ultimately do harm and precipitate renal impairment.

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Computed tomography in acute left colonic diverticulitis

Sir

I read with interest the article by Ambrosetti *et al.* (*Br J Surg* 1997; 84: 532–4) concerning acute left colonic diverticulitis. In this and previous papers[1,2] Ambrosetti *et al.* clearly demonstrated that the incidence of severe diverticulitis, as diagnosed by computed tomography (CT), was higher in patients who were operated on during hospitalization. In contrast, the incidence of mild diverticulitis as diagnosed by CT was lower in patients who were successfully treated medically The difference was statistically significant[2].

The authors conclude that 'elective colectomy may be advised after a first attack of acute left diverticulitis. .in patients whose initial CT scan revealed the prognostic signs of severity described' and that 'CT can predict medical treatment failure during the first acute manifestation of diverticulitis'[2]

In response to these papers and their conclusions I would like to make two points First, I would have been interested to have the opinion of the late Thomas Bayes about these conclusions[3]. He may have suggested not to confuse specificity, sensitivity and predictive values. In a patient hospitalized with acute left colonic diverticulitis, the data from Ambrosetti *et al.* show that the CT positive predictive value of medical treatment failure and early operation was 30 per cent[2]. I respectfully suggest that CT is not a valuable tool for assisting the surgeon in making a decision for early resection in this condition and the best tool seems to be a 'wait and see' policy.

Second, I do not understand why they observed 19 patients diagnosed as having mild diverticulitis by CT who were operated on between October 1986 and January 1992[1] and only ten patients between October 1986 and June 1995[2].

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Author's reply

Sir

I am not sure I quite understand the confusion between specificity, sensitivity and predictive values used to predict medical treatment failure This work has clearly shown that 76 per cent of patients with medical treatment failure have severe diverticulitis on initial computed tomography. If it is true that a positive predictive value to predict medical failure is 30 per cent, the same radiological investigation has a positive predictive value of 96 per cent for medical treatment success when acute diverticulitis is moderate. In this latter situation, it is a 'wait and sit' rather than a 'wait and see' policy.

The second point is correct and the text should have read nine, not 19, patients.

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Contraindication for the use of neostigmine in colonic pseudo-obstruction

Sir

An 87-year-old man was admitted as an emergency with abdominal pain, distension, vomiting and constipation. Two days previously he had been discharged from a neighbouring hospital following a 2-week admission for acute abdominal pain, for which no cause was found He had had a duodenal ulcer diagnosed 20 years ago.

His abdomen was markedly distended; there was no tenderness and no bowel sounds present. He had a raised white cell count ($16{\cdot}8 \times 10^9$/l), urea level (11·2 mmol/l) and creatinine concentration (162 µmol/l) A plain abdominal film showed dilated small and large bowel. A Gastrografin (Schering Health Care, Burgess Hill, UK) enema did not demonstrate an obstructing lesion.

A diagnosis of acute colonic pseudo-obstruction (Ogilvie's syndrome) was made, with mild renal impairment as a predisposing cause. The patient was treated with nasogastric suction and intravenous fluids. There was no improvement after 2 days and he was, therefore, given neostigmine 2.5 mg. There was a rapid response with passage of flatus and faeces and relief of abdominal distension.

Six hours later the patient had signs of peritonitis. Abdominal ultrasonography confirmed the presence of free peritoneal fluid. At laparotomy there was a large perforated duodenal ulcer and biliary peritonitis. The ulcer had been sealed by a plug of greater omentum that had been displaced by the vigorous peristaltic contractions of the transverse colon. A Pólya gastrectomy was performed, but unfortunately the patient died from septic shock 12 h after surgery.

Pseudo-obstruction of the large bowel is not uncommon in the ageing population and treatment with neostigmine has been advocated due to its parasympathomimetic action[1]. In this patient the pseudo-obstruction was the result of an ileus secondary to peritonitis confined to the supracolic space. Neostigmine should not be used if there is the possibility of a recently sealed-off duodenal or colonic perforation being unplugged by strong peristalsis.

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Myths in management of colorectal malignancy

Letter 1

Sir

I read with interest the paper by Kohler *et al* (*Br J Surg* 1997; 84: 248–51) and their attempt to dispel perceived myths about the management of colorectal malignancy.

I was particularly intrigued by the suggestion that an abdominoperineal excision would automatically include a wide mesorectal excision. This suggests some misunderstanding of the principles of total mesorectal excision, as currently practised.

Many surgeons, during an abdominoperineal excision, ligate the so-called lateral ligaments of the rectum, with the aid of large artery forceps. This inevitably leaves tissue on the side wall of the pelvis, incorporated in the ligature, which would be taken with the specimen if a total mesorectal excision were performed. At the other extreme, it would be perfectly possible to perform an abdominoperineal excision of the rectum using a technique similar to the close perimuscular dissection used by some surgeons for rectal excision for inflammatory bowel disease, which would leave the whole of the mesorectum in the pelvis.

Kohler *et al.* raise the question as to why there is no difference in recurrence rate between abdominoperineal excision of the rectum and anterior resection in previously published studies. The answer to that specific question is simple: the mesorectal dissection in both sets of patients would have been identical and neither group would have had a mesorectal excision.

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Letter 2

Sir

We enjoyed reading the article by Kohler *et al.* The points raised for debate are valid and well argued on the basis of published studies. With regard to wide mesorectal excision, however, the authors appear to assume that abdominoperineal resection (APR) 'automatically includes wide mesorectal excision' and therefore question why the local recurrence rate parallels that of anterior resection without mesorectal excision. Not only can APR be carried out within total mesorectal excision but this was routine practice until the value of complete mesorectal excision in rectal cancer was realized[1–3]. This assumption is, therefore, unfounded and any conclusions drawn from it must be viewed with scepticism.

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Letter 3

Sir

In the February edition, Kohler *et al.* argue that the oncological standards of colorectal surgery remain far from being scientifically proven and imply that the future of surgery for colorectal cancer may be better served by laparoscopic approaches. These carry the theoretical advantage of less immunosuppression. The authors cite only those articles that support their premise and commit serious interpretive errors in evaluating articles that do not do so. There are also gaps in the principles which are at the foundation of present oncological standards. Two examples will be cited.

The authors argue against the effectiveness of the no-touch isolation technique of Turnbull *et al.*[1] and cite a 58 *versus* 38 per cent 5-year survival rate for patients with positive nodes. These results could be attributed to the obligatory wide mesenteric resection that follows ligation of the named arterial and venous blood supply at their origins or apices.

Coincidentally Wiggers *et al*[2] disproved the value of initial vascular pedicle ligation and confirmed the value of a wide mesenteric resection, which was performed in both experimental and control groups. For node-positive patients, the 5-year survival rate of the 'no-touch' group was no different from that in the control group, in both cases exceeding 50 per cent. Kohler *et al.* failed to note that these and others' results represent a 150 per cent improvement in survival rate when compared with the widely reported 5-year survival rate of only 25–40 per cent for patients with positive nodes after conventional or segmental resection, techniques that ignore the principles of a complete mesenteric resection. They fail to cite other studies that demonstrate similar or better results[3] and fail to appreciate that the studies by Wiggers *et al.* have confirmed the advantages of a complete mesenteric resection for colonic cancer, while stating that there was no difference in outcome whether or not Turnbull's practice of initial vascular ligations was followed.

The issue is fundamental to the arguments in favour of or against laparoscopic resection. Protagonists argue that 'the same' operation can be carried out laparoscopically. Current studies confirm that pathology parameters of specimens resected by either approach are virtually identical but we know of few centres where a radical resection to the origin of the mesenteric vessels is being practised routinely by the laparoscopic technique. Most laparoscopic and open resections are associated with a segmental resection, without emphasis on the completeness of the mesenteric resection. The survival advantage of complete mesenteric excision for Dukes B and C cancers is being dismissed or abandoned by those advocating the laparoscopic approach and by some on the grounds of a perceived immunological advantage. There is no greater immune modulator than the complete resection of all known tumour including its potential areas of spread.

The second issue addresses a common misconception based on an older evolutionary article by Heald *et al.*[4] based on total mesorectal excision (TME) and the risk of finding cancer deposits in the distal mesorectum. Kohler *et al.* fail to cite recent articles, such as that of MacFarlane *et al.*[5], that summarize Heald's more recent results or that of Enker *et al.*[6] with a 5-year survival rate of 74 per cent and local recurrence rates of only 5–8 per cent after TME for the most common subsets of node-positive rectal cancer.

The goal of these operations must be the complete excision of the affected portion of the rectum and the mesorectum intact and contained within the visceral layer of the pelvic fascia with negative lateral margins of resection. The principle may be better expressed by complete circumferential mesorectal excision (CCME).

Kohler *et al.* do not understand why there should be an advantage to TME (or CCME) over conventional operations and ask, 'why is the local recurrence rate after abdominoperineal resection, which automatically includes wide mesorectal excision, as high as the recurrence rate after anterior resection without mesorectal excision (8–22 per cent and 11–23 per cent respectively)?'. This statement suggests a common misconception on the part of many surgeons. In 'conventional' surgery, performed bluntly and blindly, the lateral edges of the mesentery are often violated by the dissecting hand and portions of the mesentery are gouged away from the rectal wall. In 30 per cent of such instances, the portions of fat that remain attached to the pelvic side walls contain involved lymph nodes or other types of spread within the mesorectum. This represents persistent disease which accounts for the clinical presentation of local recurrence on average 18 months after surgery[7]. The success of TME or CCME lies in the complete resection of all potential spread contained within the mesorectum, within the boundaries of the intact and unviolated lateral margins of resection. These margins are anatomically defined by the visceral layer of the pelvic fascia that surrounds the mesorectum and by the areolar tissue which is present in the space between the visceral and the parietal planes of the pelvic fascia. These are entirely definable and reproducible layers.

It is the circumferential margins of resection that are addressed by TME or CCME and not the longitudinal extent of the resected rectum and mesorectum. For those who are interested in existing standards of rectal cancer surgery, a summary of the Oslo Symposium has been published recently[8].

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1 Turnbull RB, Kyle K, Watson FR, Spratt J. Cancer of the colon: the influence of the no-touch isolation technic on survival rates. *Ann Surg* 1967, **166**: 420–7.
2 Wiggers T, Jeekel J, Arends JW *et al.* No-touch isolation technique in colon cancer: a controlled prospective trial. *Br J Surg* 1988, **75**: 409–15.
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6 Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of rectal cancer. *J Am Coll Surg* 1995; **181**: 335–46.
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Authors' reply

Sir

We are grateful for the interest shown by Hemingway, Abbasakoor *et al.*, and Enker and Sarlin.

The aim of our paper was to check the sense and significance of so-called oncological standards in colorectal cancer surgery. It was not to investigate whether laparoscopic tumour resection could be carried out as radically as in open techniques. When reviewing the literature we were surprised that there have been few randomized trials concerning these standards.

Total mesorectal excision (TME) for rectal cancer is currently recommended. Lateral spread is an important factor in recurrence and wide lateral resection is mandatory. No rational surgeon would perform a close perimuscular dissection for this disease.

Mesorectal tumour deposits have been reported in 31 per cent of patients undergoing curative surgery for rectal cancer. While most of these deposits were located at the level of, or proximal to, the cancer, 10–25 per cent of the patients had carcinoma in the distal mesorectum[1,2]. Heald *et al.*[3] described discontinuous mesorectal deposits up to 4 cm below the main tumour mass but this distal spread is questioned by Stelzner[4]. These data have led to the suggestion that some local recurrences occur from carcinoma in the mesorectal tissue distal to the main tumour mass. If abdominoperineal resection is performed most of the mesorectum will be resected[3] and, therefore, we would expect a difference in recurrence rate between abdominoperineal excision and anterior resection. The concept of TME or complete circumferential mesorectal excision seems logical and is based on several studies. Heald and Ryall[5] reported a local recurrence rate of only 4 per cent, Enker *et al.*[6] 7 per cent, Cawthorn *et al.*[7] 8 per cent, Dixon *et al.*[8] 6 per cent after low anterior resection and 14 per cent after abdominoperineal resection, Aitken[9] 3 per cent and Arbman *et al.*[10] 3 per cent. The pooled local recurrence rate in 1033 patients having 'optimal' operative treatment in the form of total mesorectal resection was 7·1 per cent[11], but Morson *et al*[12] in 1960 reported a pelvic recurrence rate of 8·5 per cent (52 of 609 patients).

We did not state in our paper that mesenteric excision should be abandoned on the grounds of a perceived immunological advantage.

Drs Enker and Sarlin argue that Wiggers *et al.*[13] confirmed the value of wide mesenteric resection, which was performed in both the experimental and the control group. How could they confirm the value by performing the same technique in both groups? In the paper by Wiggers *et al.* it is stated 'No special attempts were made to perform extended lymphatic dissection'. The number of resected lymph nodes was 3·8 in the conventional group and 4·8 in the no-touch isolation group. To compare the results of

Wigger *et al.*'s study with those of other clinics or with historical controls is problematic because of case selection, different tumour stage distribution, different operative techniques, different pathologists, different follow-up criteria, and so on.

The poor overall results of cancer treatment and survival rates following surgery for gastrointestinal cancers during the past 30 years must force a rethink of treatment strategies, we will otherwise be captivated by the paradigm of Kuhn[14].

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1 Joyce WP, Dolan NF, Johnston D. Reappraisal of the 5 centimetre rule of the distal excision for carcinoma of the rectum· a study of the distal intramural spread and of patients' survival. *Br J Surg* 1983; **70**: 150–4.
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Corrigendum

Endorectal repair of rectocoele revisited. G. N. Rao, N. D. Carr, J. Beynon. *Br J Surg* 1997; 84: 1034 (Letter). A fourth author, H. C. Francis, was inadvertently omitted from the original letter submitted to the Journal.

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Book reviews

Endovascular Surgery for Aortic Aneurysms

B. Hopkinson, W. Yusuf, S. Whitaker and F Veith (eds). 233 × 155 mm. Pp. 310. Illustrated. 1997. London: W. B. Saunders. £45.

Elective open repair of abdominal aortic aneurysm reduces the risk of premature death from aortic rupture. Surgery is evidence based for aneurysms more than 5·5 cm in diameter, provided the operative mortality rate does not greatly exceed 5 per cent. Endovascular surgery for aneurysms is novel, exciting and requires the acquisition of new skills by established practitioners. It has been enthusiastically embraced by fashionable vascular surgeons. Interventional radiologists and surgeons who have yet to use some of the devices improvised and marketed after Parodi's will find all they need in this book to try their hand. There are chapters on the Min Tec, Chuter-Gianturco, Endovascular Technologies, Corvita, Sydney, Ivancev-Malmo, Parodi and Perth systems, fillers on renal damage, ischaemia–reperfusion injury and colonic perfusion; and the usual vogue chapter on quality of life. Endovascular surgery can be performed most easily on small subclinical aneurysms. The operative mortality rate is currently around twice that of open repair. The immediate and early technical failure rates are high. Complications are common. The durability and efficacy of successful grafts are unknown. Try it if you must, but not on me.

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Hepatobiliary and Pancreatic Surgery. A Companion to Specialist Surgical Practice

O. J. Garden (ed.). 252 × 192 mm. Pp. 408. Illustrated. 1997. London: W. B. Saunders. Price not supplied.

This book is one volume in a series of seven under the heading of *A Companion to Specialist Surgical Practice*. Each volume takes a specialist area, the editors aiming to provide 'succinct summaries of all key topics within a specialty'. They have succeeded admirably. It is the most up-to-date textbook that I have ever read. Every important topic in hepatobiliary and pancreatic surgery is covered. Each chapter is excellent and well referenced. Most chapters put to shame existing multiauthor tomes filled with personal bias and selective bibliography, which are often hopelessly out of date by the time they are published. The editor has allowed for some divergence of views where chapters overlap, but this is one of the strengths of the book, indicating that there are different strategies in dealing with problems. I suspect this volume will have its greatest appeal to the candidate presenting for the final intercollegiate exam. It should be compulsory reading for surgeons at all levels, who have anything to do with hepatobiliary and pancreatic disease. If you are thinking of pursuing a career in this field, go out and buy this book. It is one of the best surgical textbooks that I have ever read.

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Laparoscopic Surgery in Developing Countries

T. E. Udwadia. 250 × 185 mm. Pp. 348. Illustrated. 1997. New Delhi: Jaypee Brothers Medical Publishers. US $40.

Tremendous advances in recent years in technique and instrumentation in the field of minimal access surgery have firmly established a place for laparoscopic surgery. This is now the first choice in certain routine procedures, notably laparoscopic cholecystectomy. Notwithstanding the capital intensive nature of laparoscopic surgery in the industrialized countries, the spirited enthusiasm that has greeted the technique has by no means been restricted to leading or research institutions. Before long, therefore, the impact of laparoscopy on surgical practice in the developing world must claim attention. It is not surprising that Professor Udwadia and his colleagues on the Indian subcontinent have, as a sequel to an earlier publication on laparoscopic cholecystectomy, produced this comprehensive account of experience with laparoscopic surgery in this part of the developing world. The authors have carefully considered the issue of the fragile economies of developing countries and cost-effectiveness, and are firmly of the opinion that 'both diagnostic laparoscopy and equipment for laparoscopic surgery have special significance in the developing world; the former for its greater applicability and utility, and the latter as an essential requirement of cost-curtailment by progressively better indigenization and improvization'.

The authors give general approval for laparoscopic cholecystectomy and appendicectomy as well as diagnostic laparoscopy, but indicate that laparoscopic common duct exploration, repair of hernia, gastrointestinal surgery (i.e. vagotomy and drainage, intestinal and colonic) and solid organ surgery (mainly spleen) still require to be considered as ongoing clinical trials. It is not surprising that the contributors place such emphasis on improvization: the use of a sigmoidoscopy pump for induction of pneumoperitoneum and methods devised to substitute for expensive sophisticated abdominal wall lift equipment in gasless laparoscopic surgery. This may be a step in the right direction, permitting economic and safe laparoscopic surgery in small towns, bringing the benefits of minimal access surgery to the underprivileged in many places. It needs to be stressed, however, that these devices must be monitored by careful medical audit, as safety of the poor should not be compromised.

The book is well produced, readable, well illustrated with good quality printing and paper. It provides useful background information on indications, technique, complications of laparoscopic surgery and guidelines for the management of such complications. Its content and standard of production is truly worth the price tag of 1500 Rupees (approximately US$40) it bears. It should prove useful reading for general surgeons interested in embarking on laparoscopy in the developing world.

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Notices and announcements

12–17 October 1997
Management of Emergencies and Disasters: A Multidisciplinary Approach
Stoke, UK
Information. Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

12–18 October 1997
Telemedicine and Telecare
Belfast, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

15–22 October 1997
Cancer in Children: Challenges and Controversies
London, UK
Information. Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

23–24 October 1997
2nd Nottingham International Colorectal Cancer Symposium
Nottingham, UK
Information: J. D. Hardcastle, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

6–19 November 1997
Hong Kong International Cancer Conference and Asian Pacific Cancer Congress 1997
Hong Kong
Information: Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

27–28 November 1997
31st Meeting of the Vascular Surgical Society of Great Britain and Ireland
London, UK
Information: T. Szymanska, Vascular Surgical Society of Great Britain and Ireland, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information: M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information. O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information. Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

20–24 June 1998
Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer
Terme di Valdieri, Italy
Information: G. Buccheri, Scientific Secretary, Ospedale A. Carle, 1-12100 Roccavione (CN), Italy

12–17 July 1998
XVII World Congress of the Transplantation Society
Montréal, Canada
Information. L. Felicissimo and Associates, 12449 rue Cousineau, Montréal, Québec, Canada H4K 1P9

Announcement

Trainees in coloproctology

The Inaugural Meeting of a Club for Trainees in Coloproctology from Great Britain and Ireland was held on 18 June 1997 at the ECCP Meeting in Edinburgh. The aims of the Club are to promote the interchange of information and ideas concerning training and research in coloproctology. Membership is free and all surgical trainees who have a declared specialist or subspecialist interest in coloproctology are eligible to join.

Sixty trainees attended the Inaugural Meeting which agreed a Club constitution and elected the following officers:

President: John Stebbing (Bristol)
Secretary: Tim Cook (Oxford)
Trainee Representatives: Mark Chapman (Nottingham)
Eric Drabble (Cambridge)
Stefan Plusa (Newcastle)

Those trainees wishing to register for membership and thereby receive details of Club activities should write to:

Mr John Stebbing
49 The Dell
Westbury-on-Trym
Bristol BS9 3UF

or

Mr Tim Cook
University Department of Pharmacology
Mansfield Road
Oxford OX13 3QT

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Disks

Following final approval of articles, you will be asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Please send us digital versions of your figures. Ideally, these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them Avoid using tints if possible; if they are essential to the understanding of the figure, try to make them coarse Further details can be obtained from the publisher. Disks will not be returned to authors

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The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethics committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British* Journal of Surgery of any details or photographs that might identify an individual Submit evidence of such consent with the manuscript

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* 1997; 336: 309–15, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

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Original articles should normally be in the format of introduction, methods, results, discussion Begin each manuscript with an abstract of no more than 200 words, on a separate page. There is considerable pressure on editorial space in the Journal, so lengthy manuscripts are likely to be returned to you for shortening The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Avoid discursive speculation. **Randomized controlled trials should be clearly identified as such in the title and abstract.**

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery* These articles are 600–900 words in length, address controversial topics of current interest and are supported by up to ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication An honorarium is payable on publication.

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The Editors welcome topical correspondence relating to articles published in the Journal Letters should not exceed 250 words and should be typed double-spaced.

Typescripts

Manuscripts should be clearly reproduced with adequate space for editorial notes. **Type or print the text on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to you for recasting.** Begin each section on a new page: title page, abstract, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction, methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed, (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support, and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

Print should carry an abstract of not more than 200 words on the second page of the manuscript. Break it into four paragraphs each with a clear heading. *Background.* state why the study was done, and its main aim; *Method:* describe patients, laboratory material and other methods used Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. *Results:* state the main findings of the study; include important numerical values. *Conclusion.* state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

Tables and illustrations

Submit three copies of all illustrations and tables. Type each table on a separate page with an appropriate brief title. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate on the top of the illustration. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Include explanations of symbols and shading in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented Look at recent issues of the Journal for examples of accepted layout. If a table or an illustration has been reproduced from a published work give the original source in full. Obtain permission to use published work from the original author and the publisher before submission.

Abbreviations

Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use

Numbers and units

Use the decimal point, not a comma, e.g. 5·7. Use a space and not a comma after thousands and multiples thereof, e.g. 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; we will not accept reference to unpublished communications. Cite personal communications in the text, in parentheses The first author is responsible for confirming the acceptability of the material quoted with the originator

In the text, number the references consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s), title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted), year of publication; volume number; page numbers. For example· De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66. 184–6. The sequence for the chapters of a book should be· author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example. Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications.* New York: Springer, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; 78: 782–4 In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation of data, the analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value

Analysis

Clearly describe which methods were used for which analyses, any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '$t = 1·34$, 16 d f , $P = 0·20$'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant' Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data